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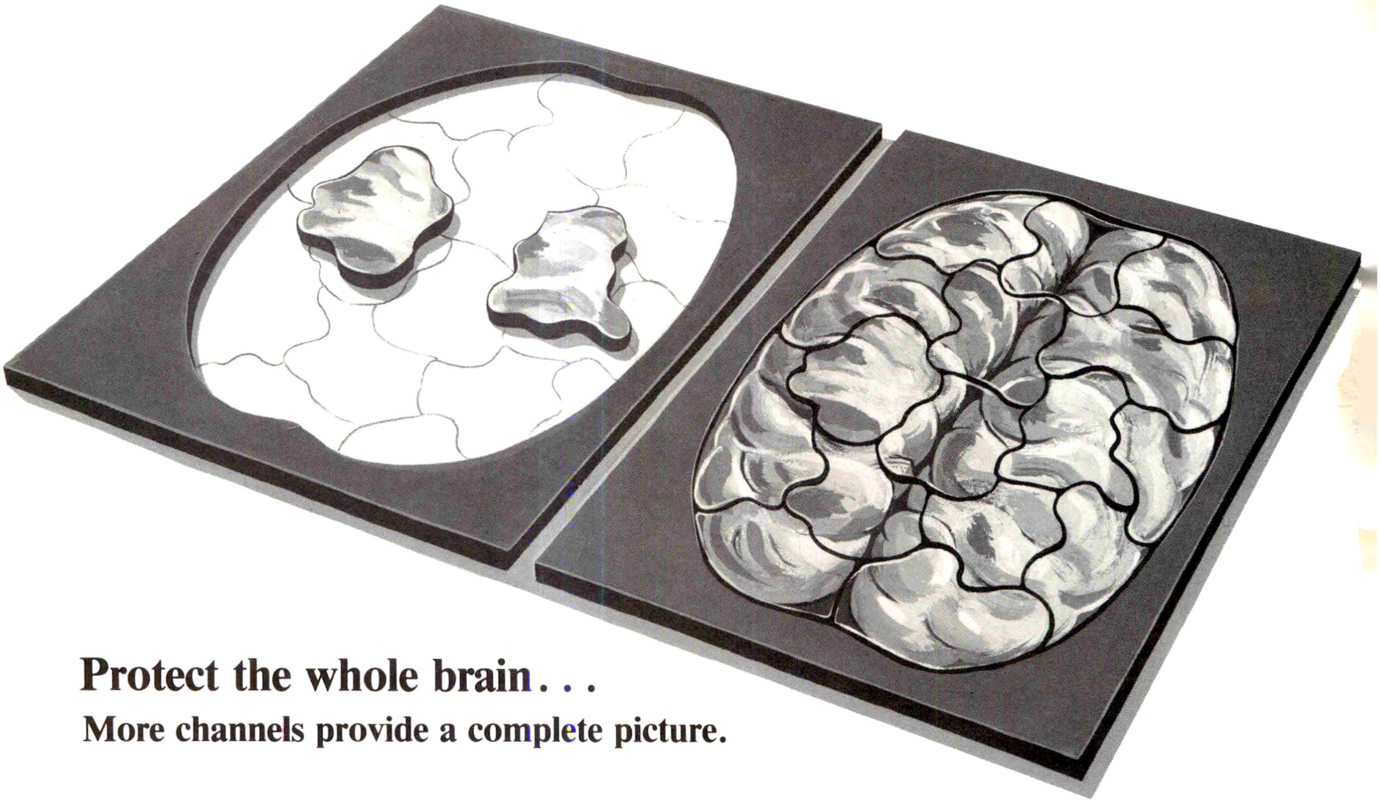

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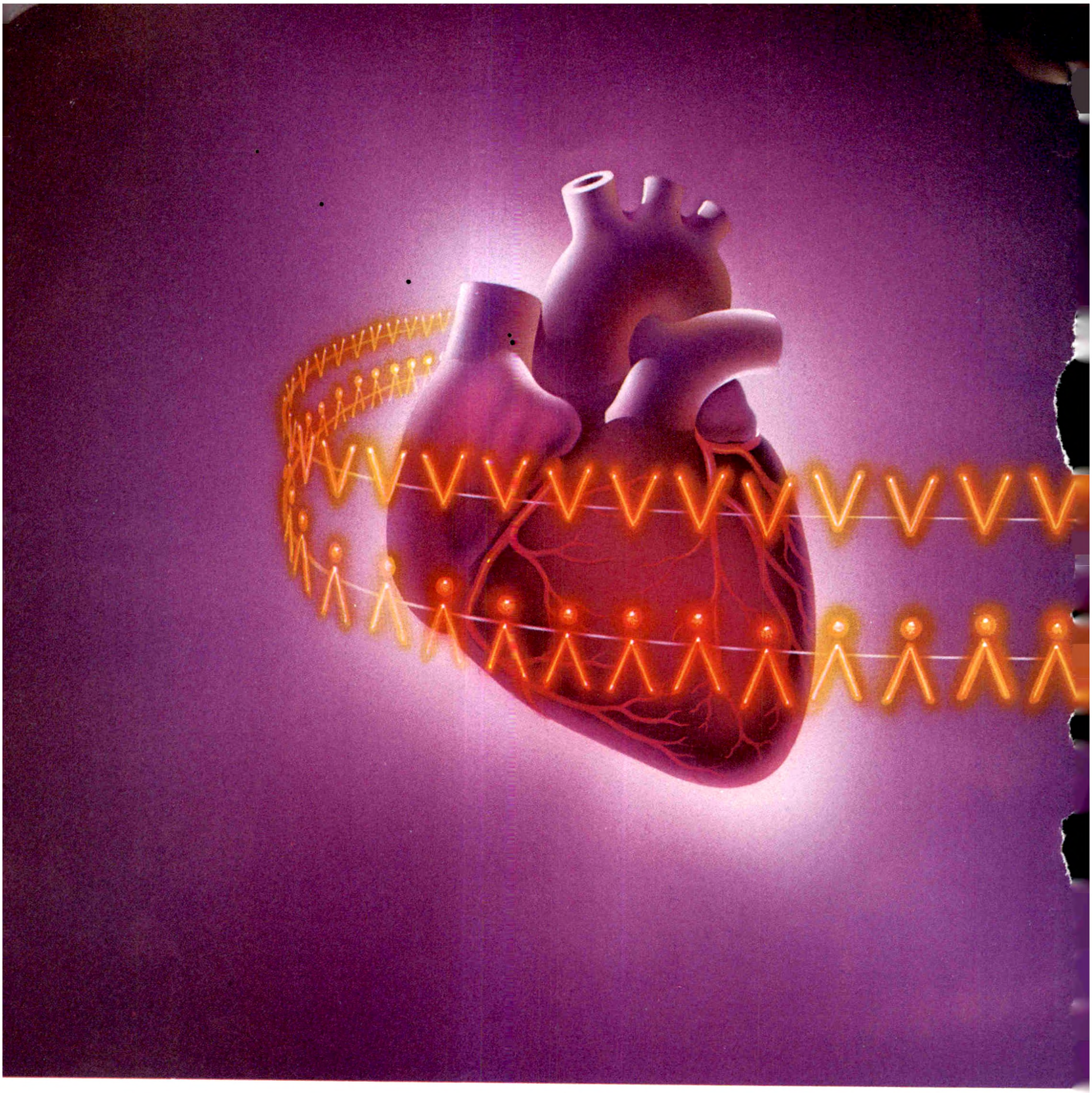

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Usage in Children: No data available pertaining to use in children.
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PRECAUTIONS
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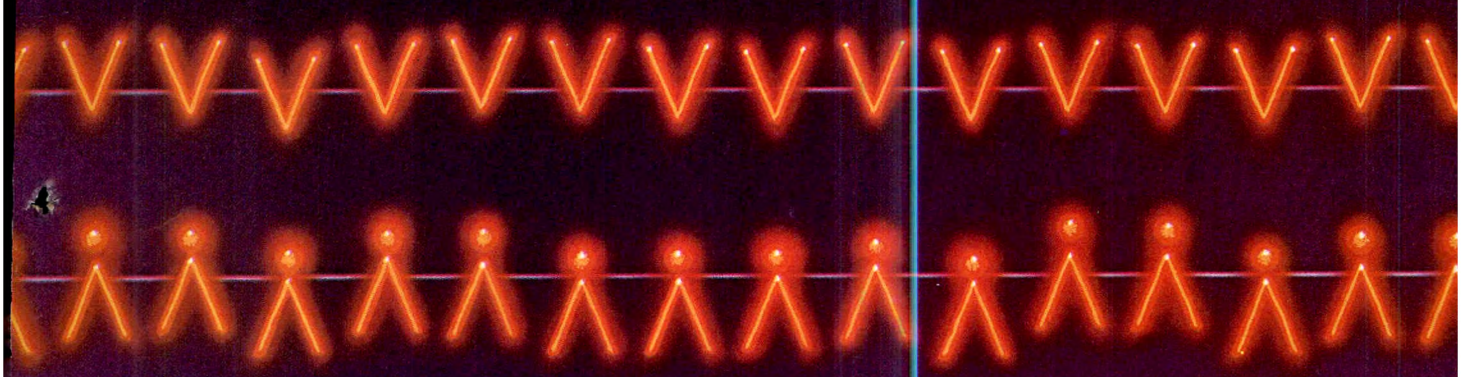

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Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

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OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

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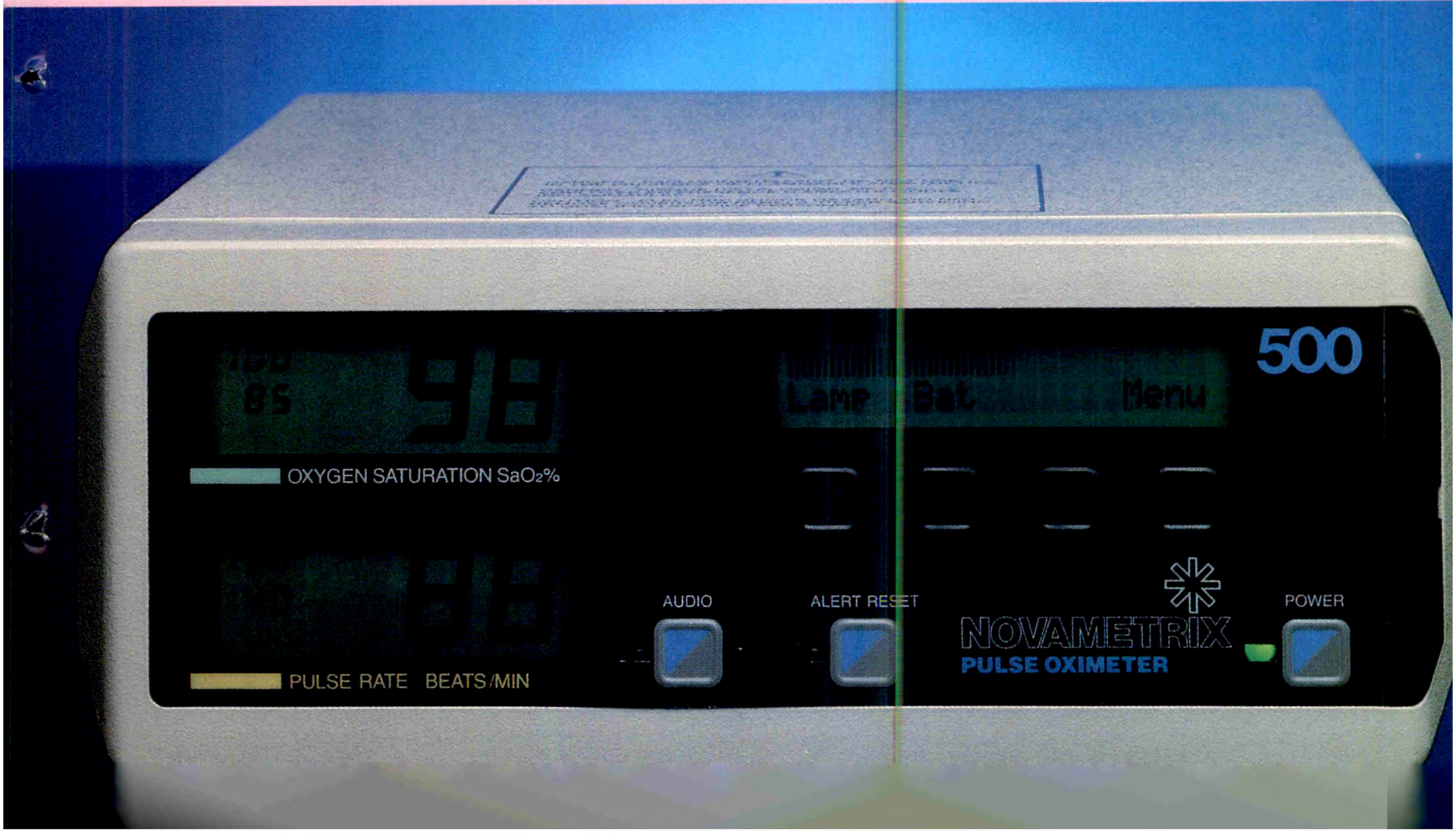
Novametrix has been out front among system manufacturers for nearly a decade, and is the **only** company that manufactures all three types of continuous O_2/CO_2 monitoring systems–Pulse Oximeter for SaO_2, Transcutaneous for O_2/CO_2 and End Tidal for CO_2. Choose the leader. Choose the Novametrix Model 500 Pulse Oximeter–the accurate, reliable early warning system. Call us toll-free at **1-800-243-3444.** Or write Novametrix Medical Systems, Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.

NOVAMETRIX



INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

61st. CONGRESS - MARCH 14–18, 1987

Buena Vista Palace Hotel, Lake Buena Vista (Orlando), Florida

PRELIMINARY MEETING INFORMATION

PROGRAM / REGISTRATION / HOTEL INFORMATION: Will be mailed in mid-December to all IARS members. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland Office: 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephone: (216) 295-1124.

MEETING SCHEDULE: Registration: Saturday, March 14, 1–6 pm (continues daily)
Scientific Program: Sunday, March 15 through Wednesday, March 18
Exhibits: Sunday, March 15 through Tuesday, March 17

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture:
John W. Severinghaus, MD–"The History of Oximetry"

REVIEW COURSE LECTURES:

- Jeffrey L. Apfelbaum, MD
- Paul G. Barash, MD
- Frederic A. Berry Jr. MD
- D. Ryan Cook, MD
- Benjamin G. Covino, MD
- Edmond I. Eger II. MD
- Mieczyslaw Finster, MD
- Betty L. Grundy, MD
- Patricia A. Kapur, MD
- Richard S. Matteo, MD
- Richard L. McCammon, MD
- Edward D. Miller Jr. MD
- Ronald D. Miller, MD
- Walter S. Nimmo, MD
- Donald S. Prough, MD
- J. Gerald Reves, MD
- Michael F. Roizen, MD
- Paul N. Samuelson, MD
- John J. Savarese, MD
- Petter A. Steen, MD
- Stephen J. Thomas, MD
- John H. Tinker, MD
- Robert W. Vaughan, MD
- Richard B. Weiskopf, MD
- Paul F. White, MD

PANEL: *Standards of Care*

- Frederick W. Cheney, MD
- John H. Eichhorn, MD
- Burton S. Epstein, MD
- William K. Hamilton, MD
- Bruce F. Cullen, MD

PANEL: *Anesthesia Equipment*

- John H. Andrews, MD
- Forrest W. Fox, MSEE
- Betty L. Grundy, MD
- A. William Paulsen, PhD
- John T. Martin, MD

136 Scientific Papers... 55 Scientific Posters... Scientific Exhibits... Theme Luncheons
Board Examinations in Anesthesiology: American Board of Anesthesiology Panel Discussion
Technical (Commercial) Exhibits - Product Seminars: Exhibitor-sponsored morning briefings

REGISTRATION • CME CREDIT • AIR TRAVEL • HOTELS

FEES:	IARS Members	$175 ($200 on site)
	IARS Educational Members	NO FEE
	Non-Members	$350 ($400 on site)
	Non-Member Residents	$50 (with certifying letter)

CME CREDIT: ACCME/AMA: Category 1–31 hours

SPECIAL AIR FARES: United and Delta Airlines, in cooperation with the IARS, will provide reduced rates for round-trip travel to Orlando. Full details will be included in the preliminary program mailing or can be obtained by calling the following numbers (8 AM to 8:30 PM EST daily) and referring to IARS meeting and code numbers shown.
Delta: 1-800-241-6760 – File No. P-0095. *UAL:* 1-800-521-4041 – Acct. No. 7015-H

HOTELS: The Buena Vista Palace and the Royal Village co-host hotel are situated in Walt Disney World Village and provide complimentary bus service to the Magic Kingdom and Epcot Center. Discounted 3- or 4-day passes will be available to IARS registrants and guests. Hotel rates are seasonally competitive, and one rate covers from single to quad occupancy.

No Rooms for Error

CAPNOGARD 1250 End Tidal CO_2 Monitor

The Technology

The Source

In the operating room and the intensive care unit, performance counts. And you can count on the Novametrix CAPNOGARD 1250 End Tidal CO_2 Monitor for reliable, sophisticated performance. It's so simple to use!

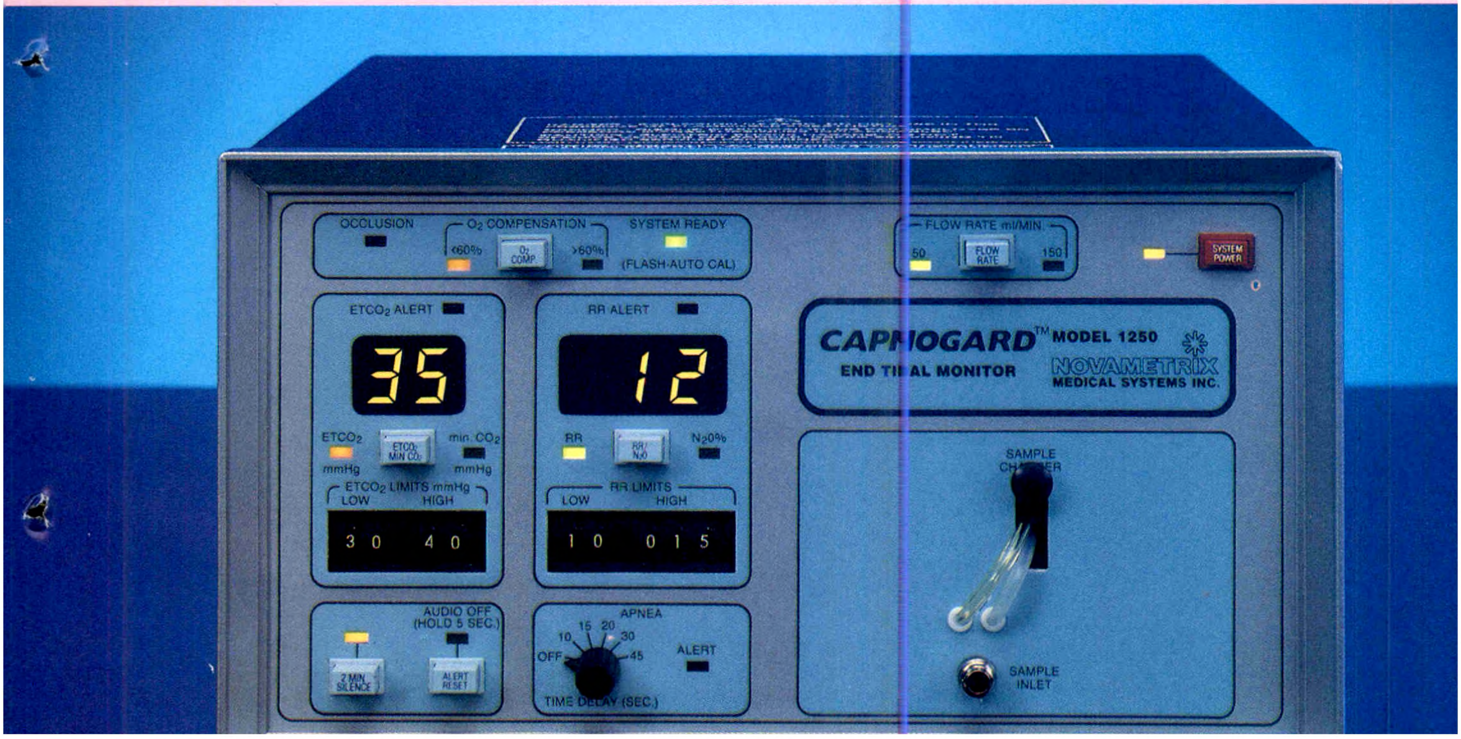
Finally, an end tidal CO_2 monitor that doesn't demand constant, complicated calibration. **Calibration is easy, and needs to be checked only twice a year.** Novametrix' exclusive auto-zeroing system assures total accuracy. Just turn on the monitor, and in two minutes, you're set to go.

Traditionally, condensation problems have plagued end tidal monitors. But not Novametrix. Our exclusive dehumidification interface kit **eliminates troublesome water traps.** But should cleaning ever be necessary, the sample cell is easily accessible from the front panel.

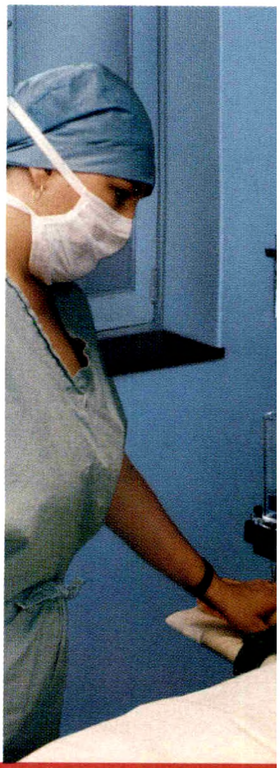
Sophisticated electronics and features like large LED readouts and continuously displayed End Tidal CO_2 values meet the toughest professional demands. One-button alarm, alert reset and two-minute silence functions were designed with the OR and ICU in mind. To provide a waveform display, the CAPNOGARD 1250 is **easily interfaced with the physiological monitor** in the OR, or to the optional NovaTracer Recorder 350 in the ICU.

Novametrix has been out front among system manufacturers for nearly a decade, and is the **only** company that manufactures all three types of continuous O_2/CO_2 monitoring systems—End Tidal for CO_2, Pulse Oximeter for SaO_2 and Transcutaneous for O_2/CO_2. Choose the leader. Choose the Novametrix CAPNOGARD 1250 End Tidal Monitor—when there's no room for error. Call us toll-free at **1-800-243-3444.** Or write Novametrix Medical Systems, Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.

NOVAMETRIX



For outpatient anesthesia



Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

Complete

Without *any* other agent or premedicant, isoflurane provides *every* action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and *ends* with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE® (isoflurane, USP)

Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or $PaCO_2$ level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest

For outpatient anesthesia

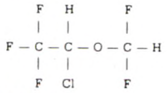
FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F{-}CF_2{-}CHCl{-}O{-}CF_2{-}H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = °C + 273.16\ \text{(Kelvin)}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C · rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

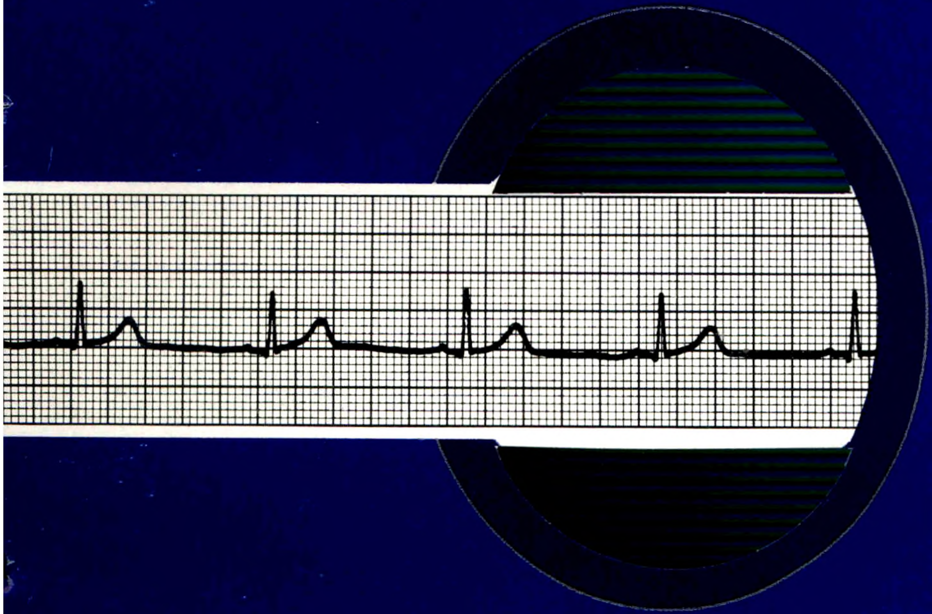
A-0336 Revised 10-85

Anaquest Forane® (isoflurane, USP)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

BOC Health Care

Heart failure
patients are often
at risk of
arrhythmias...



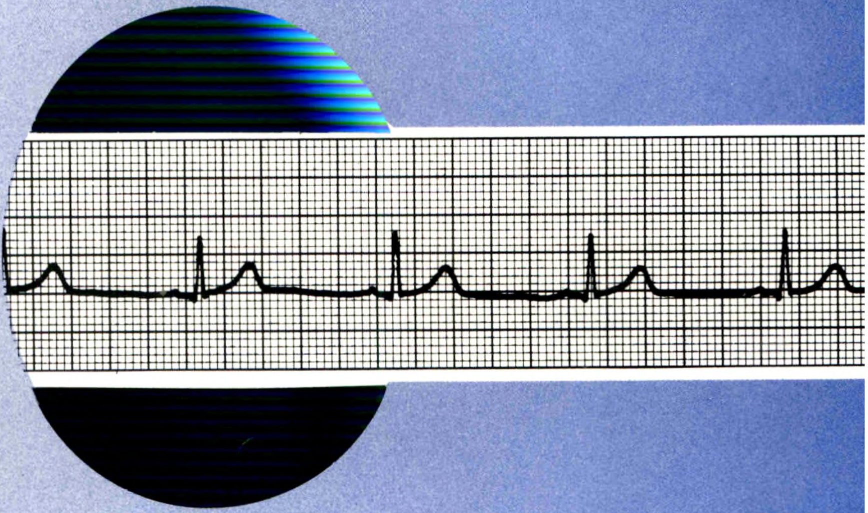
Now...
an inotropic agent
that does not significantly
increase heart rate

energy efficient

Inocor® I.V.

(AMRINONE)

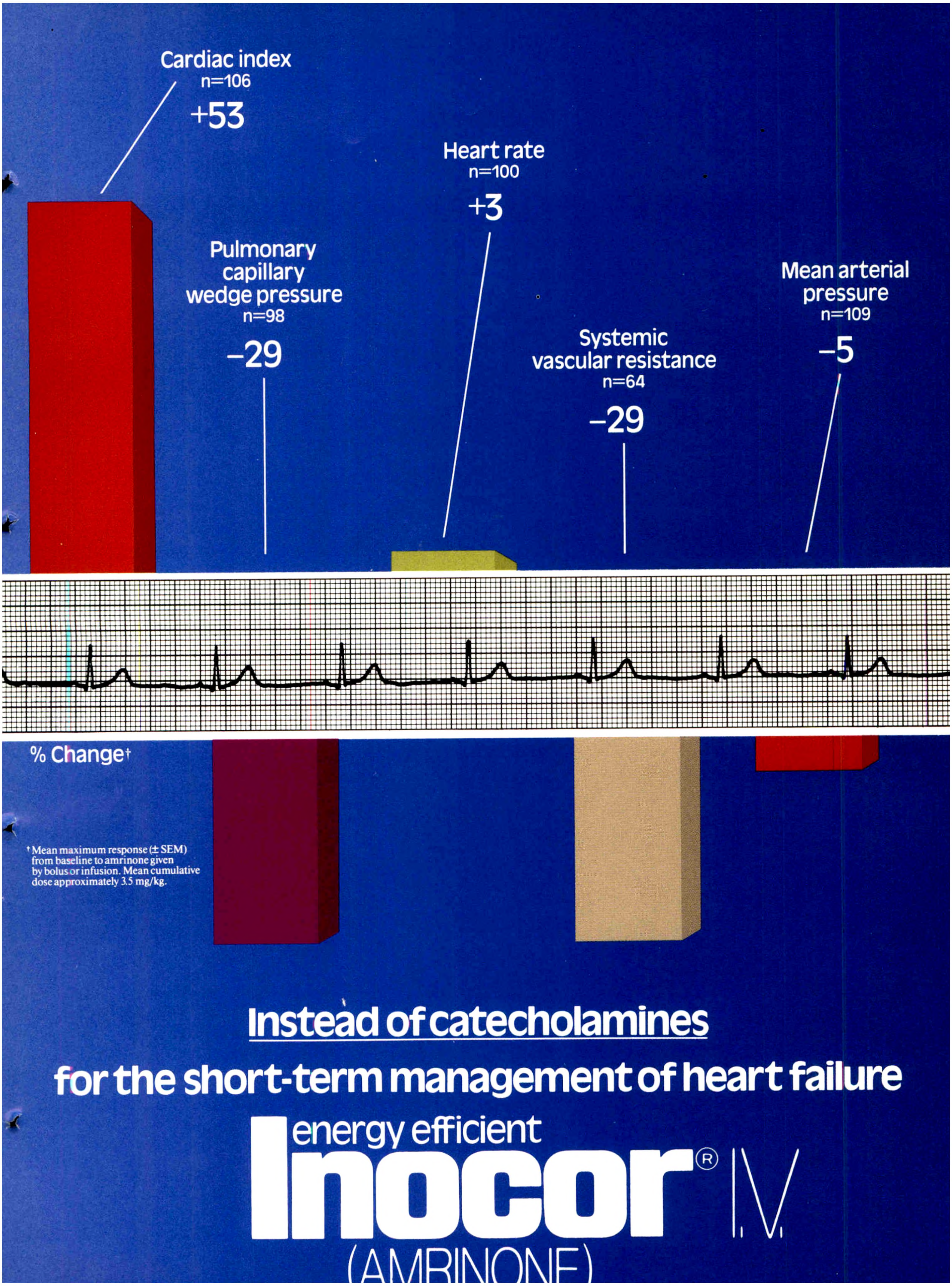
Rapidly increases cardiac output with minimal effect on heart rate or rhythm



- ○ Substantially improves contractility without adding to myocardial oxygen demand
- ○ Lowers pulmonary capillary wedge pressure and systemic vascular resistance
- ○ Heart rate and blood pressure virtually unchanged
- ○ INOCOR is intended for short-term use in patients who can be closely monitored and do not respond adequately to prior treatment with digitalis, diuretics, and/or vasodilators.

*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

© 1987 Winthrop Pharmaceuticals



† Mean maximum response (± SEM) from baseline to amrinone given by bolus or infusion. Mean cumulative dose approximately 3.5 mg/kg.

Instead of catecholamines

for the short-term management of heart failure

energy efficient

Inocor® I.V.

(AMRINONE)

A major advance toward better inotropic therapy

energy efficient
Inocor® IV
(AMRINONE)

Instead of catecholamines for the short-term management of heart failure

- Independent of the effects of digitalis and catecholamines
- Hemodynamics rapidly improved
- Heart rate and blood pressure not significantly changed... has not been shown to increase risk of arrhythmias (see precautions)
- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy... no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop PHARMACEUTICALS

Winthrop Pharmaceuticals, Division of Sterling Drug Inc., New York, NY 10016 61066

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardia inotropic agents with vasodilator activity, distinct from digitalis glycosides c catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-terr management of congestive heart failure in patients who can be closely monitored an who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestiv heart failure. Because of limited experience and potential for serious adverse effect (see ADVERSE REACTIONS), INOCOR should be used only in patients who can b closely monitored and who have not responded adequately to digitalis, diuretics, and/c vasodilators. Although most patients have been studied hemodynamically for period only up to 24 hours, some patients were studied for longer periods and demonstrate consistent hemodynamic and clinical effects. The duration of therapy should depend o patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients wh are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General*: INOCOR lactate injection should not be used in patients wit severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Lik other inotropic agents, it may aggravate outflow tract obstruction in hypertrophi subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure an heart rate should be monitored and the rate of infusion slowed or stopped in patient showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardia filling pressure to respond adequately to INOCOR lactate injection, in which cas cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the ver high-risk population treated. While amrinone per se has not been shown to b arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itse may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERS REACTIONS).

LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and rena function should be carefully monitored during amrinone lactate therapy. Improvement i cardiac output with resultant diuresis may necessitate a reduction in the dose of diureti Potassium loss due to excessive diuresis may predispose digitalized patients t arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementa tion in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manife tations have been observed in patients in whom INOCOR lactate injection was use concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metopr lol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidon ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, hepari warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was use concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use i acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C*: In New Zealand white rabbits, amrinon has been shown to produce fetal skeletal and gross external malformations at ora doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/C rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malforma tions were seen in rats receiving amrinone intravenously at the maximum dose use 15 mg/kg/day (approximately the recommended daily IV dose for patients with conge tive heart failure). There are no adequate and well-controlled studies in pregnant wome Amrinone should be used during pregnancy only if the potential benefit justifies th potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone i administered to nursing women, since it is not known whether it is excreted in huma milk.

ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate injectio resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCO lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdomina pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR la tate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/da amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation o hepatic cell necrosis or both. Hepatotoxicity has been observed in man followin long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reaction in patients treated with oral amrinone for about two weeks. Signs and symptoms wer variable but included pericarditis, pleuritis, and ascites (one case); myositis wit interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); an vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution t amrinone is not certain, but possible hypersensitivity reactions should be considered i any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studie include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotensio because of its vasodilator effect. If this occurs, amrinone administration should b reduced or discontinued. No specific antidote is known, but general measures fo circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions*: Asympt matic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the coun may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equiva lent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.

TWO COMPLEMENTARY TITLES FROM ELSEVIER

Head Injury and the Anaesthetist

edited by **W. Fitch** *and* **J. Barker**

It is believed that the anaesthetist will continue to have an important roll to play in the *overall* care of the head-injured patient, an involvement that should go far beyond the 'provision of technical assistance in the care of the unconscious patient and of anaesthesia for surgical procedures'. The contents of this monograph will inform the anaesthetist about some of the wider aspects associated with trauma to the head, and so enable him to participate fully in the care of these patients.

CONTENTS: List of Contributors. Preface. 1. The pathology of head injury *(D. I. Graham)*. 2. The pathophysiology of head injury *(J. D. Miller)*. 3. Pulmonary function in the head-injured patient *(S. Jennett)*. 4. The clinical assessment of the head-injured patient *(G. Teasdale)*. 5. The immediate care and transportation of the head-injured patient *(S. Galbraith)*. 6. Anaesthesia and the head-injured patient *(J. Barker)*. 7. The post-operative care of the head-injured patient *(J. M. Horton)*. 8. Artificial ventilation in the management of the head-injured patient *(D. G. McDowall)*. 9. Intracranial pressure monitoring in the management of the head-injured patient *(S. Galbraith)*. 10. Extracranial injuries-facial injuries *(J. P. Vance)*. 11. Extracranial injuries-chest injuries *(A. B. M. Telfer)*. 12. The use of barbiturate therapy in the management of the head-injured patient *(H. M. Shapiro, B. J. Dunlop and L. F. Marshall)*. 13. Brain death *(W. Fitch)*. 14. Future developments in the care of the head-injured patient *(B. Jennett)*. Subject index.

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ISBN 0-444-80695-4

International Resuscitation Days

Proceedings of the 2nd International Resuscitation Days
Rome, 2 October 1985

edited by **A. Gasparetto**

The success of the first meeting of the International Resuscitation Days inspired the organization of a second symposium upon which this book is based. The two main topics of this symposium were shock and parenchymal acute respiratory failure. Once again, great interest was elicited by original contributions dealing with the most recent advances in these two fields of intensive care. The contents of this proceedings volume will certainly constitute a valuable source of information for those working in intensive care throughout the world.

Contents: **Lectures.** The ethics of intensive care *(M. Rapin)*. Oximetry in the weaning of the ventilator patient *(O. Prakash)*. **Cellular Anoxia and Shock: An Update.** The role of the mitochondrial oxidative damage in the pathogenesis of circulatory shock in humans *(C. G. Corbucci, A. Gasparetto, M. Antonelli, M. Bufi, R. A. De Blasi, and G. Crimi)*. Mechanisms and therapy of septic shock *(L. B. Hinshaw)*. Endogenous opioids and other peptides in shock, spinal trauma and stroke *(J. W. Holaday, E. W. Bernton, R. C. Kinney, J. B. Long and D. S. Malcolm)*. Thromboxanes and leukotrienes as mediators of ischemia and shock *(A. M. Lefer)*. Do leukocytes play a role in the tissue damage seen with ischemia and injury? *(D. H. Lewis)*. Oxygen radicals in the pathogenesis of circulatory shock *(G. P. Novelli)*. Endurance exercise and shock - Role of oxygen radicals and antioxidants *(L. Packer)*. Septic shock *(W. Schumer)*. **New Concepts on Respiratory Support.** True mechanisms of new techniques for respiratory support: Observation on CPAP *(G. Damia, A. Pelizzola, M. Solca, M. Cigada, and A. Elena)*. True mechanisms of the new techniques of ventilatory support: Observations on high frequency jet ventilation *(G. Damia, A. Pelizzola, M. Solca, M. Cigada and A. Elena)*. Pathophysiological considerations on special modes of ventilation in severe respiratory distress syndrome *(B. Jonson, E. Evander, B. Lachmann and P. Wollmer)*. Clinical applications of combined high frequency ventilation (CHFV) *(G. Crimi, C. Mattia, G. Conti and A. Gasparetto)*. Rationale for independent lung ventilation in unilateral pneumonia *(F. Lemaire)*. Technical modalities for the realization of independent lung ventilation (ILV) *(U. R. Borg and J. C. Stoklosa)*. Clinical application of asynchronous independent lung ventilation (AILV) *(K. Hillman)*. Index of authors.

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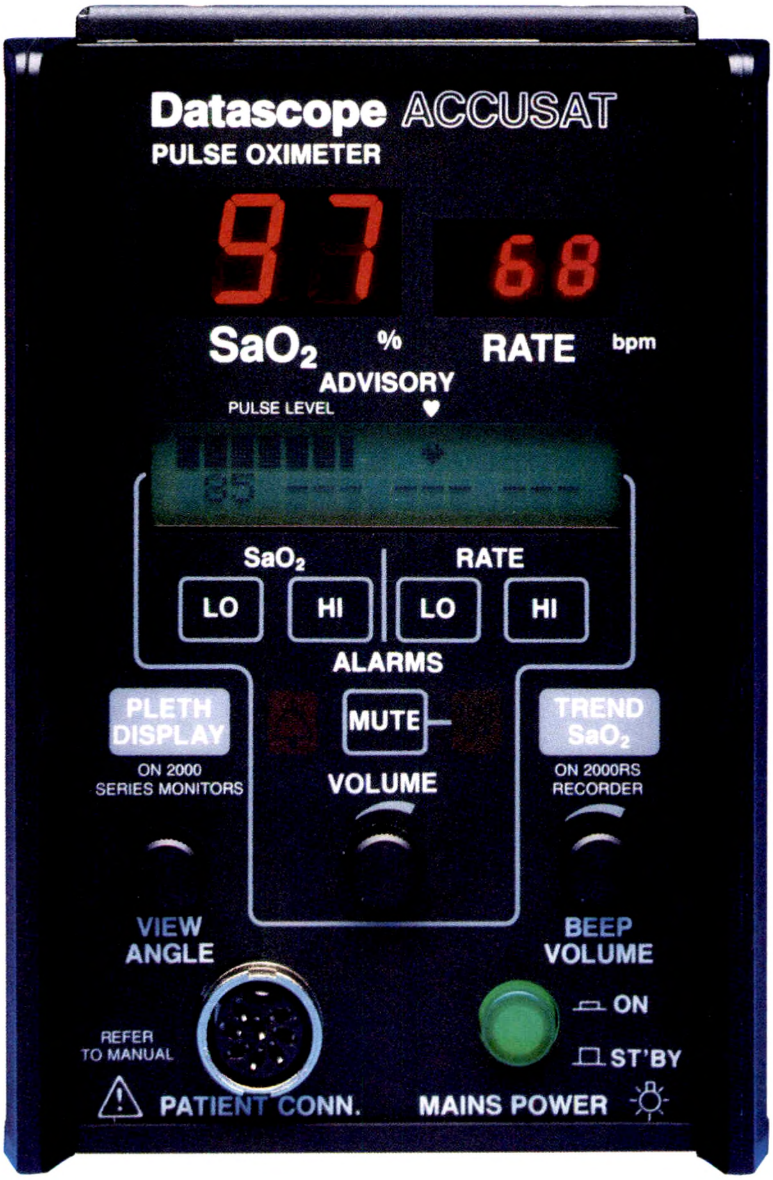

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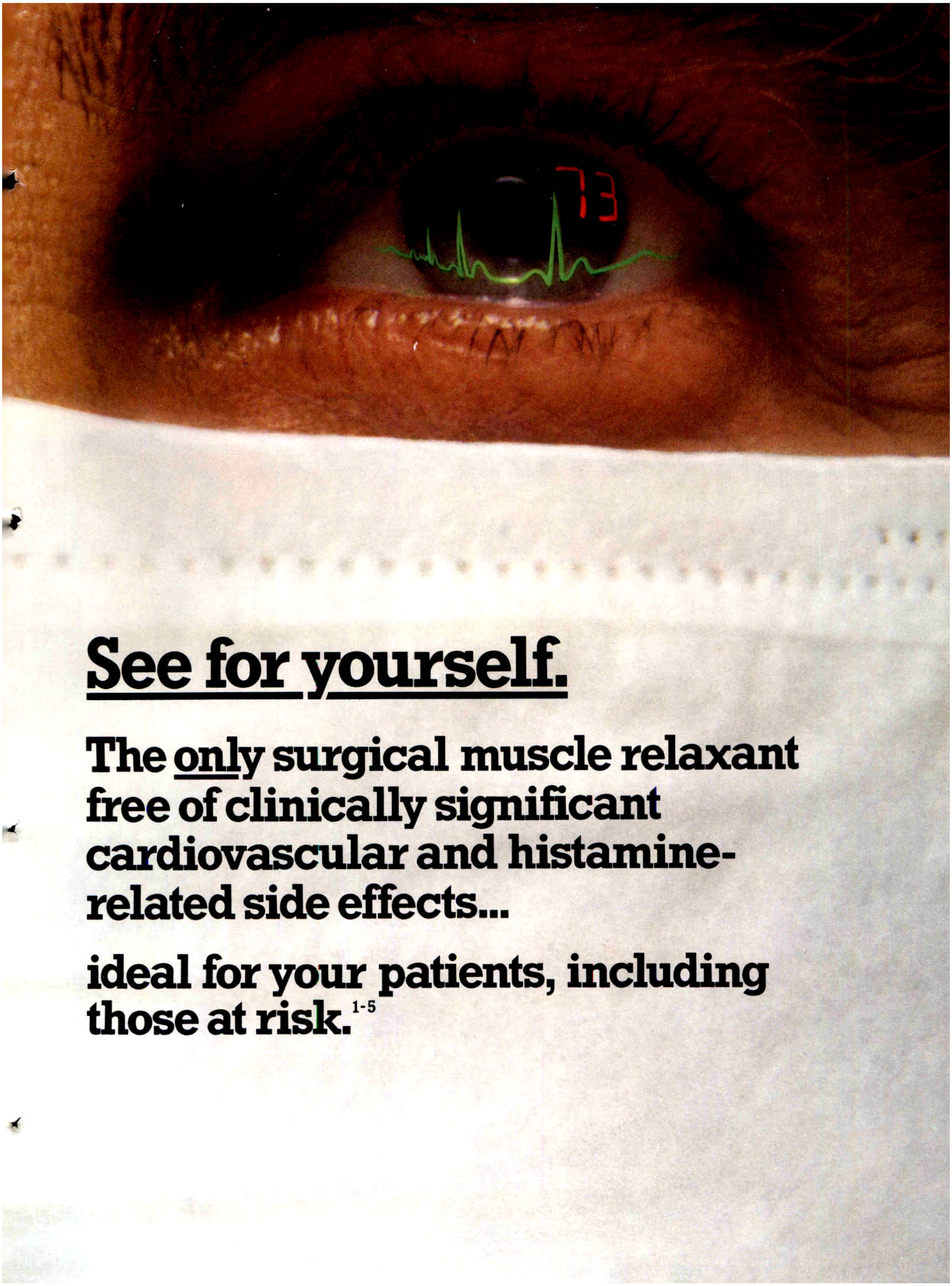
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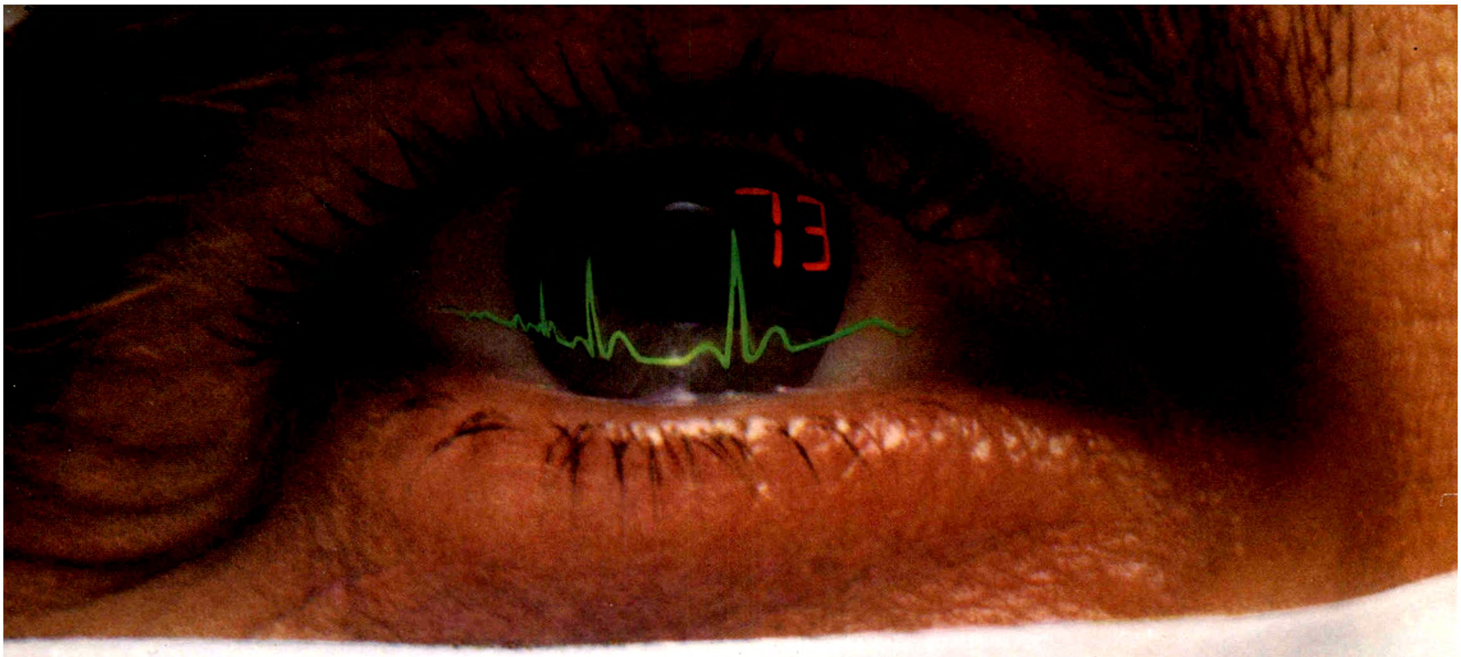
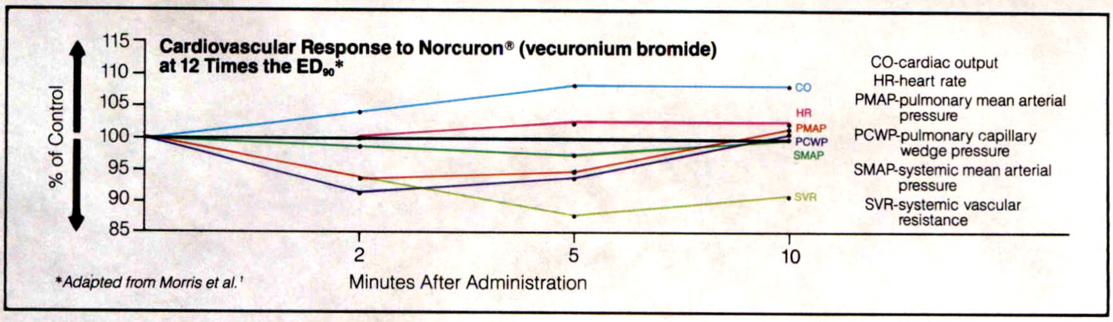
The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



*Adapted from Morris et al.[1]

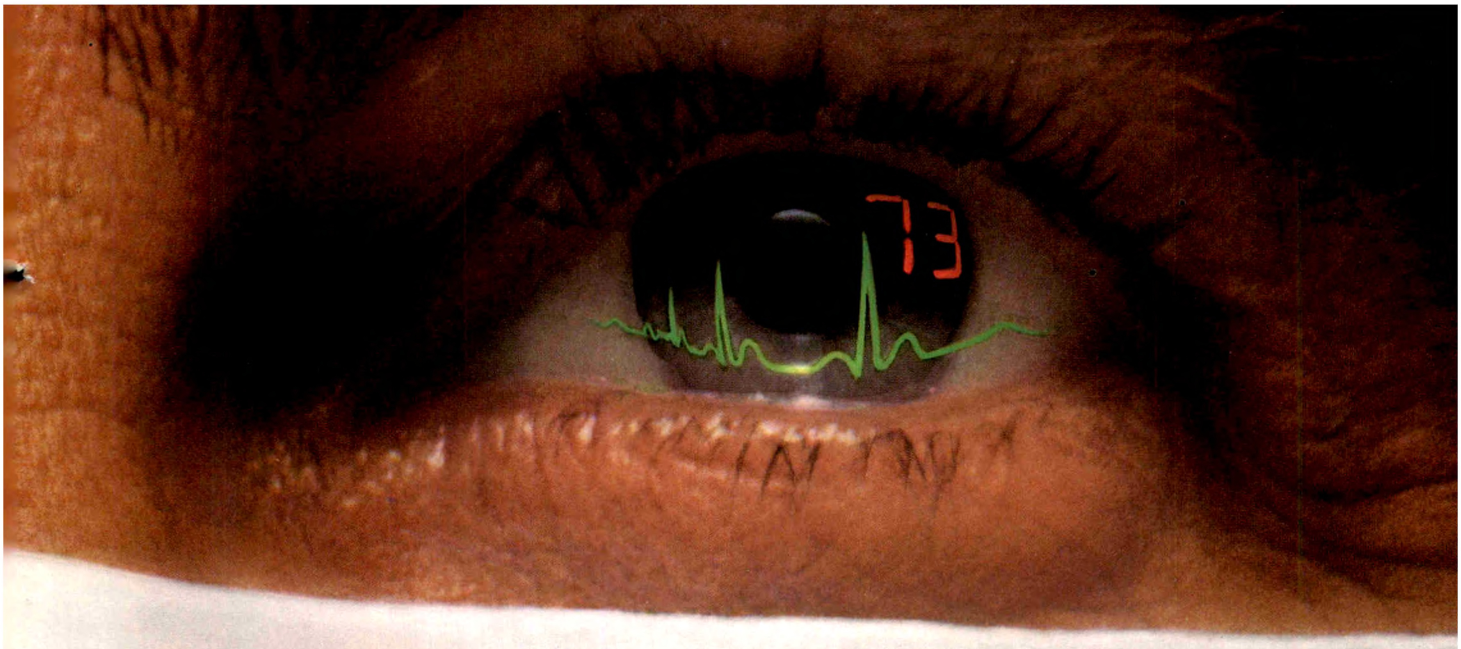
Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

Drug	Dose (mg/kg)	xED_{95}	Histamine (Percent of Control)	Mean Arterial Pressure (Percent of Control)	Heart Rate (Percent of Control)
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

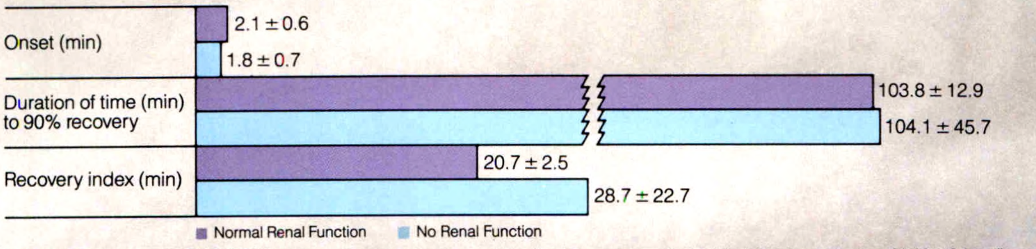
*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.

†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

NO REFRIGERATION REQUIRED

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

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Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

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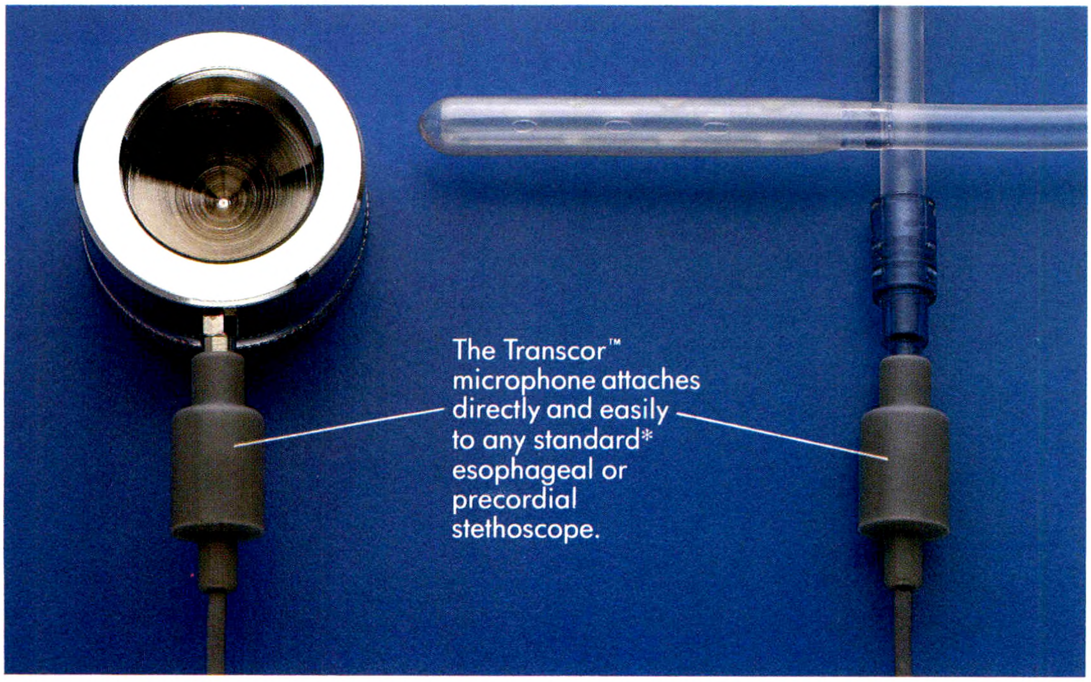

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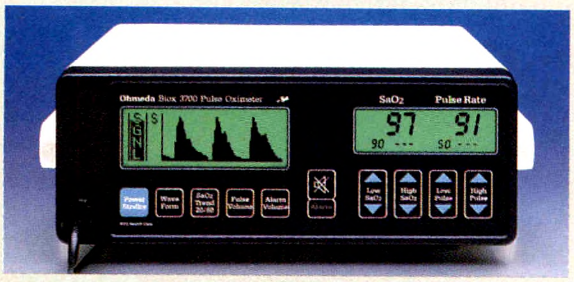

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Pharmacodynamics and Pharmacokinetics of High-Dose Sufentanil in Infants and Children Undergoing Cardiac Surgery

Peter J. Davis, MD, D. Ryan Cook, MD, Richard L. Stiller, PhD, and Karen A. Davin-Robinson, BA

DAVIS PJ, COOK DR, STILLER RL, DAVIN-ROBINSON KA. Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. Anesth Analg 1987;66:203–8.

The pharmacodynamic and pharmacokinetic profiles of high-dose sufentanil (15 μg/kg) and oxygen were determined in 20 infants and children undergoing repair of congenital heart defects. Sufentanil provided marked hemodynamic stability after an infusion and during the stress periods of incision and sternotomy. Two patients required supplemental nitrous oxide because of an increase in blood pressure greater than 20% of baseline. Mean plasma catecholamine concentrations varied widely among patients and increased, although not significantly, during intraoperative stress. Pharmacokinetic data best fit a two-compartment model. In infants younger than 10 months (group 1) and children older than 10 months (group 2) who were not surface-cooled, elimination half-lives were similar (mean ± SD, 53 ± 15 min vs 55 ± 10 min) as were clearance values (27.5 ± 9.3 vs 18.1 ± 10.7 ml·kg^{-1}·min^{-1}). However, the volumes of distribution were significantly smaller in group 1 compared with group 2 (1.6 ± 0.46 vs 3.0 ± 1.3 L/kg). In infants younger than 10 months who were surface-cooled (group 3) elimination half-life was longer (120 ± 36 min) and volume of distribution larger (3.7 ± 1.1 L/kg), but clearance rate was similar (21.5 ± 5.0 ml·kg^{-1}·min^{-1}) compared with age- and weight-matched infants (group 1).

Key Words: ANESTHESIA—pediatric. ANESTHETICS, INTRAVENOUS—sufentanil. METABOLISM—hypothermia. PHARMACODYNAMICS—sufentanil. PHARMACOKINETICS—sufentanil.

Sufentanil, a new thienyl derivative of fentanyl, is highly lipophilic and distributes rapidly and extensively to all tissues. It is five to ten times more potent than fentanyl (1,2), and in high doses can be a primary anesthetic agent for infants and children undergoing corrective cardiac surgery. In adults, sufentanil's shorter elimination half-life (3), its ability to blunt the neuroendocrine stress response (4,5), and its ability to maintain hemodynamic stability when infused intravenously (6–12) confer theoretical advantages over fentanyl. Although considerable clinical data are available about sufentanil in adults, the literature regarding sufentanil in infants and children is limited. Several investigators have evaluated the pharmacodynamic effects of sufentanil in children undergoing cardiothoracic surgery anesthetized with sufentanil and pancuronium (13,14). The direct cardiovascular action of sufentanil may have been masked by the vagolytic-like properties of pancuronium. Although the pharmacokinetics of sufentanil have been investigated in adult surgical patients (3) extrapolation of data from adults to children and infants may be erroneous because of age-related changes in body composition and drug transformation (15–17).

We therefore determined the pharmacodynamics, pharmacokinetics, and neuroendocrine stress response during high-dose sufentanil and oxygen anesthesia in infants and children undergoing repair of their complex congenital heart disease. To characterize more accurately sufentanil's hemodynamic effects, we used metocurine, a nondepolarizing muscle relaxant with minimal cardiovascular effect. In addition, we determined the effects of moderate hypothermia on the disposition of sufentanil.

Methods

Twenty infants and small children, aged 1 month to 3 yr, scheduled for elective repair of a complex congenital heart defect were studied. All infants were

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Table 1. Diagnostic Groups and Number of Patients with and without Surface Cooling

Diagnosis	Non-surface-cooled patients	Surface-cooled patients
Atrial septal defect, pulmonic stenosis	1	0
PV Obst S/P Senning	1	0
Atrial septal defect, patent ductus arteriosus, pulmonary artery hypertension	1	0
Ventricular septal defect, pulmonary artery hypertension	7	1
Transposition great arteries	1	1
Double aortic arch	1	0
Endocardial cushion defect	2	1
Ventricular septal defect	0	2
Ventricular septal defect, pulmonic stenosis	0	1
Total	14	6

Abbreviation: PV Obst S/P Senning, Pulmonary vein obstruction status post-Senning procedure.

ASA class 2 or 3. Approximately 75% were in compensated congestive heart failure controlled by digitalis and diuretics. The study was approved by the Human Rights Committee and informed written consent was obtained from a parent. Infants less than 1 yr of age were given atropine intramuscularly. The older children were premedicated with atropine, morphine, and secobarbital. The patients were divided into three groups. Patients younger than 10 months who were not surface-cooled are group 1 ($n = 7$), and similar patients who were surface-cooled are group 3 ($n = 7$). There was no statistical difference in weight, age, or surface area between groups 1 and 3. Patients older than 10 months comprise group 2 ($n = 6$). None of the older patients was surface-cooled.

The patients' diagnostic profile is shown in Table 1. Both the surface-cooled and non-surface-cooled groups included patients with right-to-left, left-to-right, and bidirectional intracardiac shunts, as well as patients with obstructive lesions. All infants and children had cardiopulmonary bypass.

The decision to surface-cool a patient was made by the attending surgeon. Anesthesia was induced and maintained as described below. After all catheters had been inserted the patient was packed in ice until core temperature decreased to 32°C. Then the ice was removed and the patient was prepared for surgery in the routine manner.

Anesthesia was induced with nitrous oxide and oxygen. An intravenous catheter was inserted and metocurine (0.3 mg/kg) was administered to facilitate tracheal intubation, to control ventilation, and to prevent chest wall rigidity. After the trachea had been intubated and an arterial catheter inserted, sufentanil (15 μg/kg) was infused over 1 min. Nitrous oxide was discontinued after the sufentanil infusion. In children in whom venous or arterial cannulation was difficult, anesthesia was maintained briefly with halothane and nitrous oxide–oxygen. Sufentanil was administered after the discontinuation of halothane and when the end-tidal halothane concentration was less than 0.10%. Anesthesia was maintained with sufentanil and oxygen. Nitrous oxide was added to control blood pressure when it exceeded 20% of baseline. The electrocardiogram (lead II) was monitored continuously and an automated blood pressure device (Dinamap) was used until radial or femoral arterial catheters had been inserted. Accuracy of the automated blood pressure device was verified with the intraarterial blood pressure recordings. Baseline vital signs were recorded on the day before surgery.

Arterial blood samples for sufentanil analysis were obtained after infusion at 1, 3, 5, 7.5, 15, 30, 45, 60, 90, and 120 min or until the initiation of cardiopulmonary bypass. The blood samples were immediately centrifuged and the plasma decanted, stored, and frozen at −60°C. The sufentanil concentrations were determined with a specific radioimmunoassay. This assay accurately detects 0.5 ng/ml of sufentanil with an interassay and intraassay coefficient of variation less than 5% over the concentration ranges measured. All samples were assayed in triplicate.

The pharmacokinetic data were analyzed with a model-dependent computation using a nonlinear regression. A computer adaptation of a manual technique for exponential stripping, ESTRIP, was used to obtain initial polyexponential estimates (18). The decay curves were fitted to the intravenous data with a nonlinear least squares microcomputer program, MULTI, with $1/CP^2$ weighing, using a modified Marquardt algorithm (19).

The decay curve for sufentanil concentration (C) vs time (t) from 0 to 90 min was evaluated, and this curvilinear form was best described by a biexponential equation. The pharmacokinetic parameters were determined by standard formulas.

Table 2. Hemodynamics during Sufentanil Anesthesia in Non-Surface-Cooled Patients

Variable	Baseline	1 Min	5 Min	Incision	Sternotom
Heart rate	140 ± 14	129 ± 25	118 ± 23[a]	116 ± 20[a]	123 ± 32
Systolic blood pressure	101 ± 9	86 ± 15[a]	74 ± 11[a]	99 ± 15	106 ± 13
Diastolic blood pressure	65 ± 10	48 ± 9[a]	46 ± 12[a]	65 ± 14	67 ± 13

Values are mean ± SD.
[a] $P < 0.01$ from baseline.

The area under the concentration curve (AUC) was calculated using the logarithmic trapezoidal rule; clearance (Cl) was calculated as Cl = dose/AUC; apparent volume of distribution (Vd_β) as $Vd_\beta = Cl/\beta$. Distribution half-life ($t_{1/2\alpha}$) as $t_{1/2\alpha} = 0.693/\alpha$; and elimination phase half-life ($t_{1/2\beta}$) as $t_{1/2\beta} = 0.693/\beta$ (multi data points).

Pharmacokinetics were measured based upon data obtained before bypass because hemodilution affects the volume of distribution. The F-ratio test was applied to the results obtained by fitting the two-compartment open model to the experimental plasma concentration time data. In all patients the weighted residual sum of the squares was not sufficiently reduced ($P = 0.05$) by the addition of a third compartment (20). Residual plots and the goodness of fit confirmed these findings.

Serum epinephrine, norepinephrine, and dopamine concentrations were measured at different intraoperative periods in eight infants, three in group 3 and five in group 1. Blood was sampled before and 4 min after sufentanil infusion, as well as 1 min after incision, 1 min after sternotomy, 1 min after aortic cannulation, and 1 and 10 min after initiation of cardiopulmonary bypass. Catecholamine concentrations were determined by radioenzymatic assay. The assay uses catechol-o-methyl-transferase to transfer a ^{3}H-methyl group from S-adenosyl-L-methionine-[^{3}H-methyl] to the catecholamines. The ^{3}H-methyl derivatives of the catecholamines are separated by thin layer chromatography, extracted, and oxidized to ^{3}H-vanillin. Radioactivity attributable to each catecholamine is determined by scintillation counting. Radioactivity in each extract is proportional to the amount of the catecholamine. The sensitivity of this method in plasma is 2 pg/50 μl for both norepinephrine and epinephrine and 15 pg/50 μl for dopamine. The coefficient of variation within runs and between runs is 4.2% and 7.5%, respectively.

Statistical Analysis

Statistical comparisons of both hemodynamic and catecholamine data were performed by repeated measures of analysis of variance followed by a Scheffe test ($\alpha = 0.05$) to determine the significance of any changes between two time periods. The pharmacokinetic dat were analyzed by both parametric one-way analysi of variance and nonparametric, Wilcoxon method Values of $P \leq 0.05$ were considered significant (21)

Results

The cardiovascular changes attributable to sufentan in patients not surface-cooled are summarized in Ta ble 2. The patients who were surface-cooled are n included because of the difficulty in separating th hemodynamic effects of hypothermia from those c sufentanil. Sufentanil caused a statistically significar reduction below baseline levels in heart rate 5 mi after injection and 1 min after sternotomy. Systoli and diastolic blood pressure decreased significantly and 5 min after infusion. With incision and sternc tomy the values returned to baseline. Two patien required supplemental nitrous oxide to control a greate than 20% increase in blood pressure. In both instance the addition of 50% nitrous oxide eliminated the hy pertensive response.

Table 3 summarizes the pharmacokinetic data i 19 of the 20 patients. In one patient (group 3) studie early in the series, gross hemolysis occurred in bloo samples during the sampling period for sufentani Because of sufentanil's ability to bind to erythrocyte hemolysis could alter plasma sufentanil concentra tions. Therefore this patient was excluded from th analysis of the pharmacokinetic data. There were sta tistically significant differences in the pharmacok netic profiles among these three groups.

The elimination half-life was statistically differer between groups 1 and 3 and between groups 2 an 3. The volume of distribution in groups 1 and 3 an 1 and 2 was statistically different as well. No statistic difference could be demonstrated in the clearance va ues among the three groups.

Table 4 lists the catecholamine levels at variou stress points during the operative procedure. A though there was a trend of increasing catecholamin concentration with decreasing sufentanil plasma cor centration, the large variability among patients pr cluded statistical significance.

Table 3. Pharmacokinetics of Sufentanil in Infants and Children Undergoing Cardiac Surgery

Group[a]	Age (months)	Weight (kg)	SA (m^2)	$t_{1/2}\beta$ (min)	Vd_β (L/kg)	Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)
1 ($n=7$)	5.2 ± 2.1	5.3 ± 1.1	0.31 ± 0.05	53 ± 15	1.6 ± 0.46[c]	27.5 ± 9.3
2 ($n=6$)	15.5 ± 5.2	8.9 ± 1.6	0.44 ± 0.04	55 ± 10	3.0 ± 1.35	18.1 ± 10.7
3 ($n=6$)	5.1 ± 3.4	5.3 ± 2.4	0.30 ± 0.09	120 ± 36[b]	3.7 ± 1.1	21.5 ± 5.0

Values are mean ± SD.

Abbreviations: SA, surface area; $t_{1/2}\beta$, elimination half-life; Vd, volume of distribution; Cl, clearance.

[a] Group 1, non-surface-cooled and aged < 10 mo; group 2, non-surface-cooled and aged ≥ 10 mo; group 3, surface-cooled.

[b] Different from groups 1 and 2 ($P < 0.05$).

[c] Different from groups 2 and 3 ($P < 0.05$).

Discussion

The cardiovascular effects of sufentanil have been studied in both adult and pediatric surgical patients. At 10–15 μg/kg doses of sufentanil, cardiovascular and hormonal stability are well maintained. For example, in patients with good left ventricular function on high doses of β-adrenergic blockers, sufentanil produced no significant change in hemodynamic stability. De Lange et al. (6) compared equipotent doses of fentanyl and sufentanil and noted that the incidence of hypertension necessitating vasodilator therapy was less in patients anesthetized with sufentanil. In the hypertensive patients supplementary doses controlled blood pressure better with sufentanil than with fentanyl. However, in a double-blind study by Rosow et al. (9) the two drugs were comparable with regard to hemodynamic stability. The hemodynamic aspects of sufentanil have also been studied in infants and children undergoing repair of complex congenital heart defects (13,14). In these studies the hemodynamics of sufentanil were evaluated in the presence of pancuronium as the muscle relaxant. Although minimal cardiovascular effects from this combination were noted by Hickey and Hansen (13), Moore et al. (14) noted a significant increase in blood pressure and heart rate from this combination. Because of the potential tachycardia and hypertension associated with pancuronium, in our study we used metocurine, a nondepolarizing muscle relaxant with minimal cardiovascular effect. We were thus able to define more accurately the hemodynamic effects of sufentanil.

As in the studies of de Lange et al. (6) and Hickey and Hansen (13), we noted a statistically but not clinically significant decrease in systolic and diastolic blood pressures within 5 min of the sufentanil infusion. With incision and sternotomy, blood pressure returned to baseline levels. Likewise, heart rate decreased after sufentanil infusion but returned to baseline rates with sternotomy. Only two patients in our series needed supplemental nitrous oxide. In the study by Moore et al. (14) increases in blood pressure and heart rate occurred during intubation, sternotomy, and incision after bolus infusions of 5, 10, or 20 μg/kg of sufentanil. Other investigators (6,7) have noted an inverse relation between sufentanil dose and the hemodynamic stress response. Our study dose of 15 μg/kg was intermediate in the range of the three doses used by Moore et al. (14), yet suppressed the hemodynamic stress response more effectively than even the 20 μg/kg dose in that study. The use of pancuronium, a nondepolarizing muscle relaxant with known cardiovascular side effects, may account for the increases in blood pressure and heart rate in the study by Moore et al.

Other explanations for the differences in the hemodynamic effect may be related to the patient population. The patients in our study were considerably younger (age range, 0–23 months) than those of Moore et al. (4–12 years) (14). Because cardiovascular function and structure change with age (22), sufentanil's hemodynamic effect may be age-related. Along with differences in age, differences in the cardiac reserve and in the nature and complexity of the underlying congenital heart defect may account for the hemodynamic disparity between our patients and those of Moore et al. Adults with compromised ventricular function often require less anesthesia for a given surgical stimulus. Further support for the influence of age and cardiac complexity on the hemodynamic changes that occur with bolus sufentanil is offered by the comparable patient profiles and cardiovascular changes in our study and that of Hickey and Hansen (13). The hemodynamic data were similar even though Hickey and Hansen administered less sufentanil (5–10 μg/kg) for induction and used pancuronium for the muscle relaxant.

The pharmacokinetic data on sufentanil are limited (3,23). In the study by Bovill et al. of adult general surgical patients given 5 μg/kg of intravenous sufentanil with a background anesthetic of halothane or enflurane, they found the plasma decay curve to fit a three-compartment model, with a terminal elimination half-life of 164 min (3), which is intermediate between those of fentanyl (185–219 min) and alfentanil (70–98 min) (24,25). To date, the pharmacoki-

Table 4. Catecholamine Levels during Sufentanil Anesthesia in Infants and Children Undergoing Cardiac Surgery

Sampling time	Epinephrine	Norepinephrine	Dopamine
1 min postinjection	805 ± 827	738 ± 317	328 ± 308
1 min postincision	659 ± 627	647 ± 589	188 ± 150
1 min poststernotomy	1406 ± 1220	1025 ± 640	363 ± 234
1 min into CPB	1250 ± 705	756 ± 574	305 ± 150
10 min into CPB	1622 ± 3147	861 ± 1191	419 ± 461

Values are mean ± SD.
Abbreviation: CPB, cardiopulmonary bypass.

netic data on sufentanil in children are limited. Our study analyzed the pharmacokinetics of sufentanil in patients until the time of cardiopulmonary bypass. The average time from injection of sufentanil until initiation of bypass was 90 ± 23 min in the non-surface-cooled groups and 104 ± 17 min in the surface-cooled group. These times are markedly shorter than the 8-h sampling period in adult surgical patients. Although our sampling period for non-surface-cooled patients was 1.5 times longer than the elimination half-life, a longer sampling period may have detected other compartments and a longer elimination half-life. Unfortunately, our sampling time was limited by the constraints of the surgical procedure.

The sufentanil plasma decay curves best fit a two-compartment model. Compared with values in the adult series of Bovill et al. (3), our infants and children (groups 1 and 2) demonstrated shorter elimination half-life and faster clearance; the volume of distribution in the younger patients (group 1) was significantly less than in the older children (group 2) or the adults.

Age-related changes in pharmacokinetics have been documented for other drugs. In neonates and infants the liver represents a larger portion of total body mass than it does in adults (26). The liver's microsomal mixed function oxidase enzyme activity (P450) is greater in infants and children than in adults (19). Although there are no published reports of sufentanil's metabolism in humans, animal studies indicate that sufentanil is metabolized by O-demethylation and N-dealkylation (27). Thus, the relative increase in liver mass and increased enzyme activity (microsomal P450) may account for the increased clearance in infants and children. Of interest is the smaller volume of distribution seen in the younger patients (group 1). A small volume of distribution in young patients with congenital heart disease has also been reported for fentanyl. Koren et al. have reported that the differences in volume of distribution are not age-related (28). Why patients with congenital heart disease have a small volume of distribution remains open to speculation, but it may be attributable to changes in α-1-acid glycoprotein (AAGP) level, changes in protein binding, or alterations in tissue receptor affinity. At pH 7.45, sufentanil is highly protein-bound, 90% AAGP and 57% albumin (29). Thus, small changes in binding will have a pronounced effect on free-drug fraction and, therefore, volume of distribution. Why these parameters may be altered in patients with congenital heart disease requires further investigation.

In addition to the age effect, we have demonstrated an effect of temperature on the kinetics of sufentanil. Surface cooling (group 3) markedly prolonged the elimination half-life and increased the volume of distribution. Others have reported similar effects of temperature on drug kinetics (30,31). Kadar et al. (30) noted in brain-injured children receiving phenobarbital that a reduced rate of metabolism, a decreased volume of distribution, and an increased elimination half-life occurred when the patients were cooled to 31–32°C. In kinetic studies of *d*-tubocurarine in cats subjected to hypothermia, the elimination half-life increased, the clearance decreased, and volume of distribution did not change (31). Infants and children, with a large surface-to-volume ratio, are particularly susceptible to intraoperative hypothermia. Therefore, temperature effects may need to be considered when administering sufentanil in children.

The endocrine and metabolic effects of sufentanil anesthesia have been studied by numerous investigators. In adult patients undergoing open heart surgery sufentanil prevents the metabolic response in the prebypass period, but cannot suppress the catecholamine surge during bypass. In pediatric patients Moore et al. (14) noted statistically nonsignificant changes in plasma catecholamine level during the stress periods of intubation, incision, and sternotomy. However, the lack of statistical significance was attributed to major individual variability. We, too, noted large variability among patients. The mean values delineate a trend after sufentanil infusion of marked decline in catecholamine levels over time; with decreasing sufentanil plasma levels, catecholamine values increased. As in other studies the bypass period was associated with increased catecholamines; however, because of the large variability among patients statistical significance could not be documented.

In summary, we have documented the safety and efficacy of sufentanil in infants undergoing repair of complex congenital heart lesions. Sufentanil reliably suppressed major changes in blood pressure and heart rate. Compared with adults (3), infants and children with cardiac disease have higher clearance rates and shorter elimination half-lives. Whether these pharmacokinetic differences can be attributed to age-related changes in hepatic function or to the study design (short sampling period) will require further pharmacokinetic studies.

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Effect of Total Spinal Anesthesia on Arterial and Venous Responses to Dopamine and Dobutamine

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To test whether acute denervation alters the vascular effects of dopamine and dobutamine, we anesthetized 16 greyhounds and placed them on total cardiopulmonary bypass (CPB). Eight dogs received total spinal anesthesia before drug testing; eight dogs were tested in the absence of total spinal anesthesia. During dopamine and dobutamine infusions, venous capacitance [determined by the volume of the CPB venous reservoir (VR)] and mean arterial pressure (MAP) were monitored. The CPB pump flows remained constant throughout our studies. Every dog received six increasing doses of both drugs. In the absence of total spinal anesthesia, both dopamine and dobutamine increased VR (decreased venous capacitance) in a dose-dependent manner. Dobutamine decreased MAP in a dose-related fashion but dopamine had no significant effect on MAP. After total spinal anesthesia, both dopamine and dobutamine produced greater dose-related increases in VR (i.e., decreases in venous capacitance) than in the absence of spinal anesthesia. Dopamine increased MAP but dobutamine had no significant effect. These data demonstrate how dopamine and dobutamine differ in their effects on the arterial circulation in the presence or absence of spinal anesthesia. The acute denervation of spinal anesthesia altered venous and arterial dose-response relationships of both drugs. Finally, our study demonstrates the effectiveness of dobutamine and, perhaps even more so, dopamine as possible alternatives to ephedrine for the pharmacologic correction of the noncardiac circulatory sequelae of spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES—spinal. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dopamine, dobutamine.

Introduction

When circulatory reflexes are prevented chronically, whether by drugs (1), toxic chemicals (2), or surgical nerve section (2,3), responses to a vasoactive drug may differ from those measured in a fully innervated preparation. In this study, by administering dopamine and dobutamine to 16 anesthetized dogs on total cardiopulmonary bypass (CPB), eight of which were tested during total spinal anesthesia, we attempted to determine whether the acute denervation of total spinal anesthesia alters the noncardiac circulatory effects of vasoactive drugs.

Methods

Sixteen adult greyhounds (sex was immaterial) weighing 26.3 ± 0.3 kg (SEM), not used in prior experiments were anesthetized with intravenous thiopental (25 mg/kg), intubated, and mechanically ventilated with oxygen-enriched air. Anesthesia was maintained with intravenous pentobarbital, 1 mg/kg every hour after an initial 5 mg/kg dose. Femoral arterial and venous cannulae were inserted. A 19-gauge epidural catheter was inserted through a 17-gauge Weiss epidural needle into the cisterna magna of eight randomly chosen dogs; its correct placement was confirmed by free flow of cerebrospinal fluid from the catheter. The spleen was excised to eliminate changes

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in reservoir volume due to catecholamine-induced contraction of its muscular capsule (4). The abdominal wound was closed. A median sternotomy was performed and heparin (4 mg/kg) was administered into the right atrium. The CPB circuit was primed with 2 L lactated Ringer's solution. Cannulae in the superior and inferior venae cavae, a right-sided transventricular vent, and a clamp on the pulmonary artery ensured complete diversion of cardiac venous return into a calibrated reservoir approximately 30 cm below the right atrium. Normothermic CPB was initiated at a flow of 75 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ using a Sarns (Ann Arbor, Mich.) model 1800 bypass pump and Shiley (Irvine, Calif.) model S100A oxygenators. The heart was fibrillated with topical ice.

Animals received either a constant infusion (25 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) or bolus injections (between studies) of intravenous Ringer's lactate to replace evaporative and "third space" losses. We used the latter method of fluid administration in the initial experiments ($n = 4$) of this study; thereafter, to simplify analysis of VR data, animals ($n = 12$) were given a constant infusion, the amount of which (25 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) was the mean fluid requirement of animals in the early phase of this and previous experiments (5). Arterial pH and oxygen and carbon dioxide tensions were maintained within normal ranges (7.35–7.45, > 80 mm Hg and 35–45 mm Hg, respectively), and were kept constant during drug testing by altering CPB pump gas flows or, when rarely necessary, by administering intravenous sodium bicarbonate. Hematocrit values determined after initiation of CPB and at the termination of the experiment averaged 31 ± 1% (SEM) and 30 ± 1% (SEM), respectively. The maximal decrease in hematocrit was 5%; the mean decrease was 1%. One dog was eliminated from the study because of excessive intraabdominal bleeding.

After cardiovascular steady state (defined as less than 10% variation over a 10-min period) was reached and baseline mean arterial pressure (MAP) (55 ± 5 mm Hg (SEM)) and venous reservoir (VR) (1460 ± 50 ml (SEM)) were recorded for all 16 animals, drug testing began in the eight animals not receiving spinal anesthesia. The other eight animals received hyperbaric tetracaine via the cisternal catheter (20 mg in 5% dextrose, total volume 4 ml) to induce total spinal anesthesia and tetracaine hourly (10 mg in 5% dextrose, total volume 2 ml) to maintain spinal anesthesia. The MAP and VR were again recorded when these eight dogs reached cardiovascular steady states (28 ± 2 mm Hg (SEM) and 1350 ± 160 ml (SEM), respectively), and drug testing was begun. The delay (roughly 10 min) attendant on onset of spinal anesthesia produced negligible changes in baseline hemodynamic values in previously studied animals without spinal anesthesia. Testing in nonspinal anesthesia animals, therefore, was not postponed to compensate for this small delay.

Table 1. Hemodynamic Effects of Dopamine and Dobutamine in Dogs with Intact Spinal Reflexes

Dose[a] ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	Change[b] in MAP (%)	Change[b] in VR (ml/kg)
Dopamine ($n = 8$)		
Baseline values: MAP 56 ± 4 mm Hg; VR 1420 ± 120 ml		
1	3 ± 2	0.2 ± 0.6
2.5	3 ± 3	1.3 ± 0.6
5	5 ± 3	2.0 ± 0.8
10	−0.1 ± 4	2.8 ± 1.9
20	1.8 ± 6	3.6 ± 1.3
50	18 ± 7	6.3 ± 2.4
Dobutamine ($n = 6$)		
Baseline values: MAP 72 ± 6 mm Hg; VR 1080 ± 250 ml		
1	2 ± 4	−0.3 ± 0.4
2.5	1 ± 4	0 ± 0.3
5	−8 ± 6	1.1 ± 1.4
10	−20 ± 7	3.1 ± 1.8
20	−35 ± 6	4.3 ± 2.1
50	−43 ± 4	4.8 ± 2.0

Values are means ± SEM.

[a] Each dose administered for 5 min.

[b] Compared with baseline steady-state values immediately before first dose of each drug.

In each of the 16 dogs, six increasing doses of both dopamine and dobutamine were given (Table 1); all doses were administered with an infusion pump into the arterial port of the CPB reservoir. Drug doses were chosen to bracket the clinically relevant range for each agent. Each infusion was maintained for 5 min to ensure that a steady state had been reached, even though pilot studies had demonstrated no differences between data recorded after 3-, 5-, or 10-min infusions. Drug onset times were unchanged by spinal anesthesia. MAP and VR data were recorded at the end of each 5-min infusion. Dopamine and dobutamine were given in either order, with each animal receiving all (increasing) doses of one drug before any doses of the other drug were given. To limit bypass time, hemodynamic variables were not allowed to return to baseline between doses of a drug. However, the animal was rested for at least 10 min to establish a new steady state before testing with the second drug began, and testing did not begin until both MAP and VR had reached steady state. Total bypass time did not exceed 90 min. No dog showed progressive acidosis or other signs of deterioration during the study period.

In the eight animals not receiving spinal anesthesia, baseline steady-state MAP and VR values recorded before any drug was given were compared with steady-state measurements recorded after each 5-min infusion of the first drug. In the eight animals receiving total spinal anesthesia before drug testing, steady-state values measured after spinal anesthesia were compared with steady-state measurements recorded after each 5-min infusion of the first drug. In both groups, baseline values for the second drug were obtained during the "rest period" following the first drug and were compared with values after each 5-min infusion of the second drug.

Reservoir volume and MAP dose-response data were subjected to "growth curve" analysis to test for a significant dose-related effect. [Growth curve analysis tests the null hypothesis that there is no relationship between drug dose and drug effect, without necessarily attempting to define the relationship between the two (6).] The data were entered in a VAX 730 computer (Digital Equipment Corporation, Maynard, MA) and analyzed using routines in the Statistical Analysis System (SAS Institute, Cary, NC). The relationships between the outcome variables (change in MAP and change in VR) and the drug doses of dopamine and dobutamine were estimated by fitting each dog's data to a series of exponential curves and to straight lines using standard regression routines. This first stage of the analysis yielded a line, the estimated slope and intercept of which related drug dose to outcome variables. Of particular interest in this study were the estimated slopes, which were interpreted as the estimated average change in the outcome variable corresponding to a unit change in dose, or the dose-response rate, for each dog. Statistically significant dose-related drug effects were identified when mean slopes deviated significantly from 0 (the null hypothesis of non-dose dependence). Each dog received both dopamine and dobutamine and one "anesthetic" (spinal versus nonspinal)—thereby defining four exclusive data groups. In each of these four categories, the average dose response for the group and the *t*-test were employed to test if the group (on average) showed a positive or negative response to increasing drug dose.

Analysis of variance (ANOVA) was employed to test for differences attributable to the drug (dopamine versus dobutamine) and to the anesthesia (spinal versus nonspinal). A standard 2 × 2 factorial design was assumed. The interaction between drug and anesthesia was tested, and if found to be nonsignificant, removed from the model to obtain a pooled estimate of the differences between drugs and anesthesia approaches.

Table 2. Hemodynamic Effects of Dopamine and Dobutamine in Dogs with Ablated Spinal Reflexes (Total Spinal Anesthesia)

Dose[a] (μg·kg^{-1}·min^{-1})	Change[b] in MAP (%)	Change[b] in VR (ml/kg)
Dopamine (n = 7)		
(Baseline values: MAP 27 ± 1 mm Hg; VR 1650 ± 170 ml)		
1	−3 ± 2	0.4 ± 0.8
2.5	0 ± 1	0.1 ± 2.1
5	11.7 ± 1.8	0.8 ± 2.6
10	12.4 ± 3.5	2.7 ± 2.8
20	23.9 ± 5.7	8.6 ± 1.3
50	48.7 ± 8.6	12.4 ± 2.4
Dobutamine (n = 8)		
(Baseline values: MAP 28 ± 2 mm Hg; VR 1500 ± 130 ml)		
1[c]	−0.2 ± 1.5	1.6 ± 1.1
2.5	−0.1 ± 2.3	2.6 ± 1.2
5	1.1 ± 2.7	6.2 ± 1.8
10	8.3 ± 4.6	7.6 ± 1.6
20	10.6 ± 5.3	9.7 ± 2.0
50	10.3 ± 5.9	13.2 ± 2.9

Values are means ± SEM.

[a] Each dose administered for 5 min.

[b] Compared with baseline steady-state values immediately before first dose of each drug.

[c] n = 7 for this dosage due to lost data point.

Results

Because of deviations from the experimental protocol, all dobutamine data collected during two of the early nonspinal experiments and all dopamine data from one dog in the spinal group were excluded from analysis. The effects of the lowest dose of dobutamine were not recorded for one dog in the spinal group. In none of the 16 dogs did there appear to be an effect of drug order on drug effect.

In the absence of spinal anesthesia (Table 1), both dopamine and dobutamine increased VR; dobutamine decreased MAP in a dose-related fashion but dopamine failed to change MAP significantly. There was no apparent change in measured drug effects when testing was occasionally delayed in animals not receiving spinal anesthesia by an amount of time comparable to that required to induce spinal anesthesia; the number of animals in which delay occurred (n = 2) was insufficient to permit direct statistical comparisons.

When total spinal anesthesia had interrupted spinal reflexes (Table 2), both dopamine and dobutamine increased VR (decreased venous capacitance) in a dose-related fashion. On the other hand, only dopamine increased MAP in a dose-related fashion; dobutamine had no significant effect.

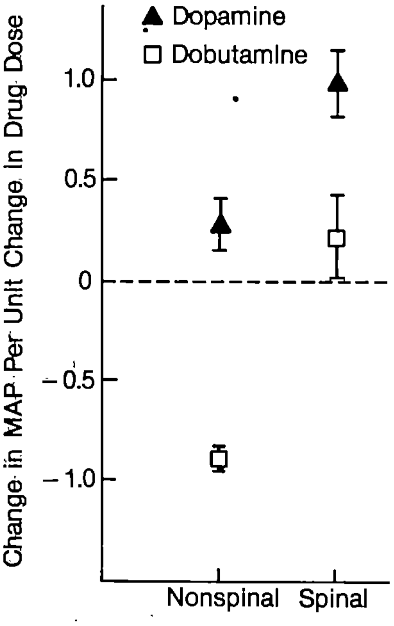

Figure 1. Average of calculated slopes (as percent μg^{-1}·kg·min) of dose–response curves; MAP recorded as percent change from baseline; drug dose in $\mu g \cdot kg^{-1} \cdot min^{-1}$.

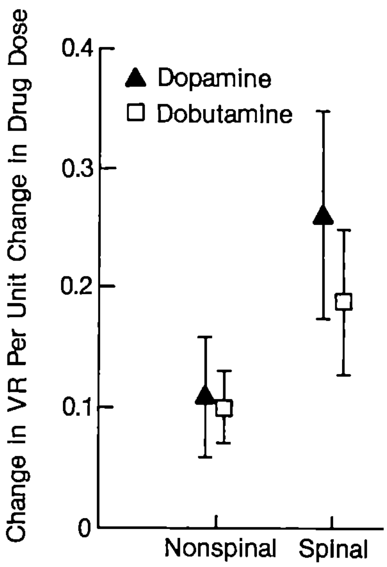

Figure 2. Average of calculated slopes (as ml·μg^{-1}·min) of reservoir volume (VR) dose–response curves; VR recorded as ml·kg^{-1} change in volume; drug doses in $\mu g \cdot kg^{-1} \cdot min^{-1}$.

MAP Slope Analysis

Figure 1 displays the slope of MAP dose-response lines for the four groups. The dopamine–spinal anesthesia group had a response rate significantly above zero ($P < 0.01$), indicating that there was increasing change in MAP with increasing dose of dopamine. For both the dopamine–nonspinal anesthesia and the dobutamine–spinal anesthesia groups, there was no evidence ($P > 0.05$) of a dose-related effect on MAP. The dobutamine–nonspinal anesthesia group showed a significant decline in MAP with increasing dose ($P < 0.01$).

No evidence of interaction between drug and anesthesia ($P > 0.10$) was identified by ANOVA, indicating that the source of the differences between the two drugs in their effects on MAP did not relate to the presence or absence of spinal anesthesia, or, conversely, indicating that spinal anesthesia modified the MAP response to both drugs in the same overall way. Therefore, it was reasonable to test for an overall drug effect (dopamine versus dobutamine) and overall anesthesia effect (spinal versus nonspinal anesthesia) by removing the interaction term in the 2 × 2 factorial.

When data were combined without regard for anesthesia, the overall MAP response to dopamine was estimated to be 0.974 above the overall response to dobutamine, a highly significant difference ($P = 0.0001$), indicating that for the pooled spinal anesthesia and nonspinal anesthesia groups there was a larger MAP increase for dopamine than for dobutamine. Also, the pooled estimated MAP response during spinal anesthesia was 0.896 above the response when spinal anesthesia was absent, again a highly significant ($P = 0.0001$) difference. This indicated that both drugs induced a larger response in the presence of spinal anesthesia than in its absence, supporting our underlying hypothesis regarding denervation and vasoactive drugs.

VR Slope Analysis

Figure 2 provides slopes of the VR dose-response lines for the four treatment groups. Each group showed significant ($P < 0.05$) increases in VR with increasing doses.

These dose-response rates showed no significant interaction between drug and anesthesia by ANOVA ($P > 0.10$), indicating that the differences between dopamine and dobutamine were consistent between spinal and nonspinal anesthesia. Likewise, the differences between the spinal anesthesia and nonspinal anesthesia responses were similar for both drugs.

When data with both drugs were combined, VR dose responses were seen to be significantly greater during spinal anesthesia than when spinal anesthesia was not used. No statistical difference was detected between the effects of dopamine and dobutamine on VR ($P > 0.10$). Data on the effect of spinal anesthesia on MAP and VR in these eight dogs were included in our previous report (5).

Discussion

This study demonstrates that dopamine and dobutamine produced different effects on MAP in dogs on CPB, whether or not total spinal anesthesia was present, although total spinal anesthesia altered the effects of both drugs on MAP. Dopamine and dobutamine increased VR whether or not spinal anesthesia was present.

We used CPB to prevent drug effects on the heart from influencing our results and to enable us to use VR at constant CPB pump flow as our index for changes in venous capacitance. At constant CPB pump flow, changes in arterial resistance were directly proportional to changes in MAP. We used total rather than fractional spinal anesthesia to ensure that sympathetic denervation was complete, an experimental paradigm more easily standardized and maintained than any less complete level of anesthesia.

In the nonspinal anesthesia group, there was greater variability in the baseline steady-state MAP obtained before each drug series than in the spinal anesthesia group. Moreover, the higher baseline MAP in the dobutamine (nonspinal anesthesia) group relative to dopamine (nonspinal) and relative to our previous data (5) (for which we have no explanation) may have introduced some bias into our analysis, making dobutamine-induced hypotension appear more profound than, in fact, it was. We do not believe, however, that any bias in the baseline would account for the dobutamine-dose-dependent decline in MAP that we measured, the slope of which differed significantly ($P < 0.01$) from the null hypothesis of a non-dose-dependent effect. Moreover, the contrast between the baseline variability of the nonspinal anesthesia group and the stable conditions obtained during spinal anesthesia supports our hypothesis that data collected from innervated preparations differ from data collected in the absence of sympathetic reflexes, such as during spinal anesthesia.

Our findings agree with those of previous studies, showing increased VR after administration of β-adrenergic agonists in the absence of total spinal anesthesia (7,8). Fuchs et al. found a dobutamine-induced decrease in vascular capacitance in an exteriorized spleen model of the canine mesenteric vasculature (the likely source of increased VR after adrenergic agonists) (9). Marino and colleagues measured significant increases in VR when patients on CPB received bolus injections of dopamine (10). Thus, despite differences in species and techniques, we expected both dopamine and dobutamine to increase VR in our model. Likewise, we expected differences between the effects of dopamine and dobutamine on MAP, since clinical and experimental studies had identified dopamine as being more likely than dobutamine to raise MAP (11–14). We confirmed these differences both in the presence and in the absence of spinal anesthesia.

Previous investigators have studied single vessels or vascular beds to compare the effects of vasoactive drugs on the arterial and venous systems (15,16). We believe that these studies may not necessarily predict the integrated responses of the entire systemic vasculature to a drug. Such measurements may not be the most appropriate criteria for selecting a drug to correct the cardiovascular sequelae of spinal anesthesia (17). In contrast, CPB techniques "sample" the aggregate response of all vessels in the systemic circulation. Furthermore, "cardiac output," or, more correctly, CPB pump flow, can be set at a constant value, so that direct and reflex drug actions on heart rate and contractility will not obscure measurements of VR. Thus, CPB techniques are well suited to the study of the influence of spinal anesthesia on hemodynamic responses to vasoactive agents.

Our model, like any other, is not an exact replica of clinical spinal anesthesia or of patients who receive dopamine or dobutamine. However, in the absence of cardiac function, differences in hemodynamic effects between high thoracic and total spinal anesthetics should be small. Sympathetic outflow is limited to thoracic and lumbar regions of the spinal cord, all of which are blocked by high thoracic levels of spinal anesthesia (17,18). Our total bypass time (<90 min) is consistent with the experimental times of others (8), and not likely to result in significant decline of the normothermic preparation. Moreover, by alternating the drug order, a time-related bias due to undetected rundown in the experimental preparation should have been prevented.

From our previous experience (5), we expected that spinal anesthesia would influence vasoactive drug effects, and this study confirms that spinal anesthesia significantly alters the effects of these drugs on MAP. How spinal anesthesia prevents dobutamine from inducing further dose-related hypotension remains unclear. Dobutamine-induced reduction of systemic vascular resistance has been attributed to its actions on β_2-receptors of arteriolar smooth muscle (11,13–15,19). The resting tone of arteriolar smooth muscle is likely to be lower in the presence of total spinal anesthesia than in its absence; further relaxation might not be detectable. Alternatively, dobutamine binding to α_1-receptors might serve to counterbalance β_2-receptor-activated vasodilation when total spinal anesthesia has already vasodilated the systemic circulation to near maximum (9,13,15).

Infusable drugs often are preferable to those that must be injected as boluses. Ephedrine, which corrects the venous pooling and hypotension that follow spinal anesthesia, is ill suited for infusion or repeated injections (11). Endogenous catecholamines released from nerve terminals produce its major effects, and repeated doses of ephedrine deplete the catecholamines and cause tachyphylaxis. Although it would be improper to extrapolate directly from our data to a clinical recommendation, we have identified two agents administered by infusion that correct the venous pooling induced by spinal anesthesia in an experimental model, and that are likely to have similar actions in human patients. Dopamine—which, during spinal anesthesia, affects VR and MAP similarly to ephedrine—might be preferable to ephedrine in cardiac patients, since the effects of its administration by infusion can be controlled more readily. During spinal anesthesia, dobutamine has advantages over isoproterenol, which we and others have identified as increasing VR (5,7,8). Unlike isoproterenol, dobutamine increases VR in doses that do not reduce MAP.

From these data, we conclude that dopamine is a reasonable therapeutic option to ephedrine for correction of the noncardiac vascular sequelae of spinal anesthesia. Dobutamine is useful when venous return, but not MAP, needs to be increased. Such a situation might occur when cardiac output decreases during spinal anesthesia employed for controlled hypotension. Venous return might be maintained with fluid administration or blood transfusion or, pharmacologically, with dobutamine. The choice among these three approaches can be based on the need to control drug dosage precisely (necessitated, for example, by significant cardiac disease) or to avoid specific drug side effects (for example, dopamine may decrease uterine and placental blood flow—making it a poor choice to treat the vascular sequelae of spinal anesthesia during cesarean delivery) (20,21). Overall, there appears to be no significant difference between the venous capacitance effects of dopamine and dobutamine in our experimental model.

From these data, we also have confirmed our contention that spinal anesthesia alters the action of vasoactive drugs. The MAP response to dopamine and dobutamine during total spinal anesthesia was not predicted by data collected when spinal anesthesia was not present. We conclude that the denervation attendant to spinal anesthesia has profound effects on venous and arterial hemodynamics and on the effect of adrenergic agonists on venous and arterial tone. Furthermore, we believe that the influence of these factors on vasoactive drug effects cannot be predicted, except when spinal anesthesia is used.

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Amrinone Blunts Cardiac Depression Caused by Enflurane or Isoflurane Anesthesia in the Dog

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MAKELA VHM, KAPUR PA. Amrinone blunts cardiac depression caused by enflurane or isoflurane anesthesia in the dog. Anesth Analg 1987;66:215–21.

The effects of two infusion rates of amrinone, a positive inotrope and vasodilator, were studied during high and low concentrations of either enflurane or isoflurane anesthesia in a canine model. The anesthetic concentrations used were: "low" = 2.1–2.2% enflurane or 1.7–1.8% isoflurane, and "high" = 3.4–3.5% enflurane or 3.0–3.1% isoflurane. The two infusion rates of amrinone were: "low" = 2 mg/kg plus 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and "high" = 4 mg/kg plus 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the present study, amrinone, in sufficient doses, blunted the deleterious effects of enflurane or isoflurane on myocardial function, reduced systemic vascular resistance (SVR) and pulmonary capillary wedge pressure, restored left ventricular dP/dt_{max} ($LVdP/dt_{max}$), and maintained cardiac index, even at the high concentrations of enflurane or isoflurane that caused marked cardiac depression. However, with reduced SVR, mean arterial pressure remained low. With lower enflurane or isoflurane, high concentrations of amrinone elevated $LVdP/dt_{max}$ and heart rate above baseline, which might be of concern if myocardial oxygen supply were limited. No arrhythmias were observed at any time in this study. Amrinone did not increase plasma catecholamine levels with either anesthetic. Elevated amrinone plasma concentrations persisted for at least 1 hr after cessation of the high amrinone infusion and continued stimulatory effects on the cardiovascular system were observed. These results suggest that in selected patients amrinone may be beneficial in the short-term treatment of perioperative depression of cardiac performance.

Key Words: PHARMACOLOGY—amrinone. ANESTHETICS, VOLATILE—enflurane, isoflurane.

Improvement of cardiac performance is a major objective in the treatment of congestive heart failure. Recent interest has focused on a new class of inotropic drugs, the prototype of which is amrinone. Amrinone is a bipyridine derivative that improves cardiac performance by a combination of positive inotropic and vasodilating properties. Intracellular accumulation of cyclic AMP resulting from the inhibition of cyclic AMP phosphodiesterase plays an important role in its action (1,2).

Amrinone may be useful in clinical circumstances associated with low cardiac output and high left ventricular filling pressure. It may be of use in patients with poor left heart function after cardiopulmonary bypass, and patients with heart failure associated with acute myocardial infarction. Also, patients with chronic heart failure may become temporarily refractory to oral medication, and short-term inotropic support may be needed to restore pump function (3,4).

Amrinone has been shown to improve cardiac performance in pentobarbital-induced heart failure in dogs and also during pentobarbital-induced heart failure in the dog heart-lung preparation (5,6). In rabbit papillary muscle, Komai and Rusy (7) showed that amrinone effectively counteracts the negative inotropic effect of halothane (1%) during single pulse (0.2 Hz) stimulation. They suggested that amrinone increases the influx of extracellular Ca^{2+} across the sarcolemma but not the availability of cellular Ca^{2+} that accumulates, most likely in sarcoplasmic reticulum, under the condition of potentiation.

Inhalation anesthetics must be used with caution in patients with impaired cardiac function because of the dose-dependent cardiac depression produced by volatile anesthetics (8). In a closed-chest dog preparation using two different levels of isoflurane and enflurane, Merin et al. (9,10) showed that both anesthetics produce myocardial depression in a dose-dependent manner but the depression appeared to be less at equipotent levels of isoflurane (low, 1.48% end-tidal; high, 3.0% end-tidal) than with enflurane (low, 2.31% end-tidal; high, 3.64% end-tidal). In a

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previous study we have shown in an enflurane-anesthetized canine model that increasing amrinone plasma levels from approximately 1 to 4 μg/ml resulted in progressive hemodynamic effects associated with decreased systemic vascular resistance (SVR) and increased cardiac index (CI) at lower levels with, in addition, increased left ventricular dP/dt_{max} ($LVdP/dt_{max}$) and decreased pulmonary capillary wedge pressure (PCWP) at higher levels (11). That study, however, included only one anesthetic at one concentration.

The purpose of the present study was to investigate the effects of two infusion rates of amrinone during high and low concentrations of enflurane or isoflurane anesthesia in a canine model to determine if the deleterious effects of high anesthetic concentrations could also be overcome by amrinone, as well as to determine the dose-related effects of amrinone during isoflurane anesthesia in the same model. Such information may help to guide the clinician in an evaluation of whether amrinone would be useful in the perioperative management of depressed myocardial performance.

Methods

At 3–4 week intervals, each of four experiments were carried out in five conditioned mongrel dogs of either sex, weighing 21 ± 1 kg (mean ± SEM). The four experiments consisted of enflurane alone (E); amrinone plus enflurane (AE); isoflurane alone (F); and amrinone plus isoflurane (AF). The dogs were anesthetized with enflurane or isoflurane in 40% oxygen in air via a chronic tracheostomy and mechanically ventilated (Harvard Apparatus Company, Model 623) to maintain Pa_{CO_2} within normal limits. To maintain pH within normal limits, $NaHCO_3$ was administered as needed, and 0.9% NaCl was infused intravenously at approximately 8 $ml\cdot kg^{-1}\cdot hr^{-1}$ to maintain adequate hydration and urine output. Temperature was maintained between 38–39°C with a warming blanket and a heating lamp. End-tidal concentrations of enflurane, isoflurane, CO_2, and O_2 were continuously measured by mass spectrometry (Perkin-Elmer, Model #MGA 1100). An arterial catheter was placed in a femoral artery for direct blood pressure measurements and blood sampling. A pulmonary artery catheter was passed via an external jugular vein for measurements of right atrial pressure, mean pulmonary artery pressure, PCWP, and cardiac output (CO), the latter in triplicate by thermodilution (Edwards Laboratory Cardiac Output Computer, Model 9520). A micromanometer-tipped catheter (Millar Instruments, Inc., Model PC 350) was placed retrogradely in the left ventricle (LV) via a femoral artery for direct LV pressure measurements and electronic derivation of LVdP/dt. The maximum LVdP/dt ($LVdP/dt_{max}$) was taken as the peak positive deflection of the LVdP/dt trace. Limb lead II of the electrocardiogram, heart rate (HR), arterial blood pressure, central venous pressure (CVP), pulmonary arterial pressure, LV pressure, and LVdP/dt were continuously recorded on a Hewlett Packard polygraph, Model 7758A. In addition, the ECG was intermittently recorded at fast paper speed (100 mm/sec) for measurement of PR intervals. Systemic vascular resistance and pulmonary vascular resistance (PVR), CI, stroke volume index, and stroke work index (SVI, SWI) were calculated. The blood samples were analyzed for plasma concentrations of epinephrine (EPI), norepinephrine (NEPI), and amrinone by high performance liquid chromatography (12,13). After 60 min of stabilization with the anesthetic (low enflurane or isoflurane), baseline cardiovascular measurements were made and blood samples taken (time 0). To test for effects of the amrinone solvent, group E received the solvent alone for 30 min in an amount equivalent to that used for the high amrinone infusion. After these measurements the protocol consisted of a series of 30-min periods (see the bottom of Fig. 1). The enflurane and isoflurane control groups, E and F, received a low concentration of anesthetic for 30 min followed by a high concentration for 60 min, after which time the anesthetic was decreased back to the lower level. In the combined groups, AE and AF, the anesthetic protocol was the same but amrinone was added at two rates for 60 min each: a low bolus plus infusion followed by a high bolus plus infusion. The anesthetic concentrations used were: "low" = 2.1–2.2% end-tidal enflurane or 1.7–1.8% end-tidal isoflurane, and "high" = 3.4–3.5% end-tidal enflurane or 3.0–3.1% end-tidal isoflurane. The bolus and infusion rates of amrinone were: "low" = 2 mg/kg plus 30 $\mu g\cdot kg^{-1}\cdot min^{-1}$ and "high" = 4 mg/kg plus 100 $\mu g\cdot kg^{-1}\cdot min^{-1}$ (IVAC 230 infusion pump, IVAC Corporation). Amrinone was freshly dissolved in the solvent for each experiment; the bolus was injected over 2 min and the infusion was started at the same time. Measurements and blood samples were repeated at 25 and 30 min of each period: period I, low enflurane or isoflurane plus low amrinone; period II, high enflurane or isoflurane plus "low" amrinone; period III, high enflurane or isoflurane plus high amrinone; period IV, low enflurane or isoflurane plus high amrinone; period V, amrinone off, low enflurane or isoflurane; and period VI, low enflurane or isoflurane. In the anesthetic alone groups, E and F, the measurements and blood samples were taken at times equivalent to 25 and 30 min of each period I to

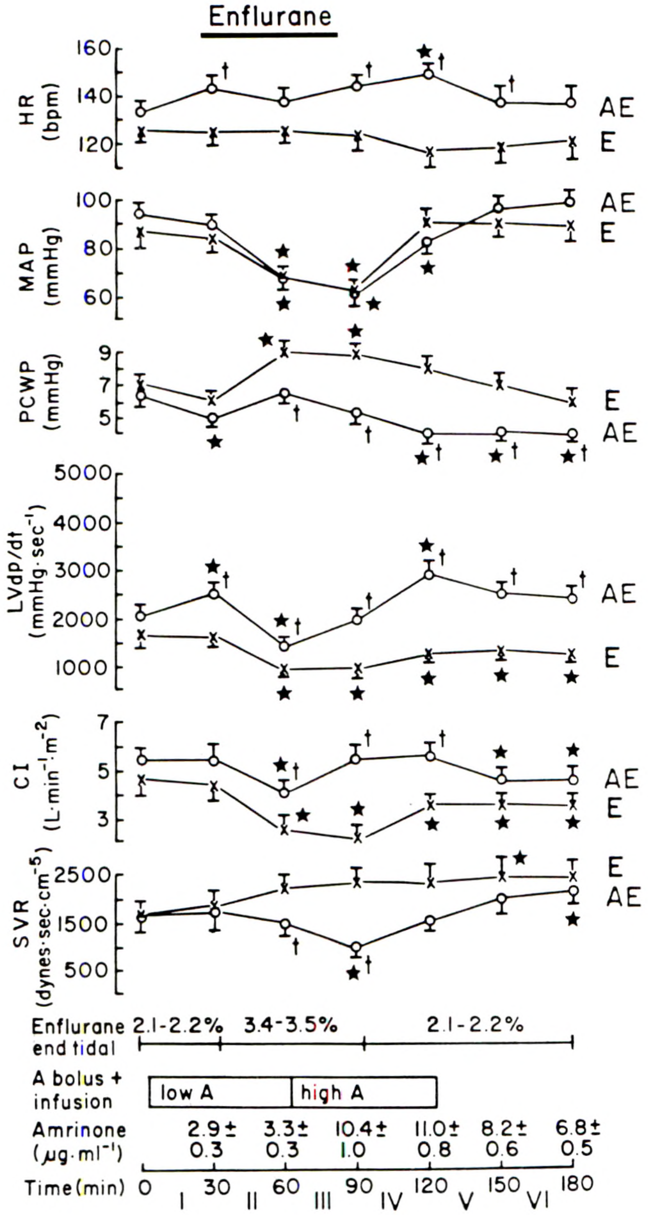

Figure 1. Hemodynamic measurements in the amrinone-enflurane (AE) group (○), and in the enflurane (E) alone group (x). Data are expressed as mean ± SEM. Symbols: $^*P < 0.05$ compared to time 0. $^†P < 0.05$ compared to the enflurane alone group. Low A and high A are the two different successive bolus and infusion rates of amrinone. Amrinone plasma levels shown are expressed as mean ± SEM (see text).

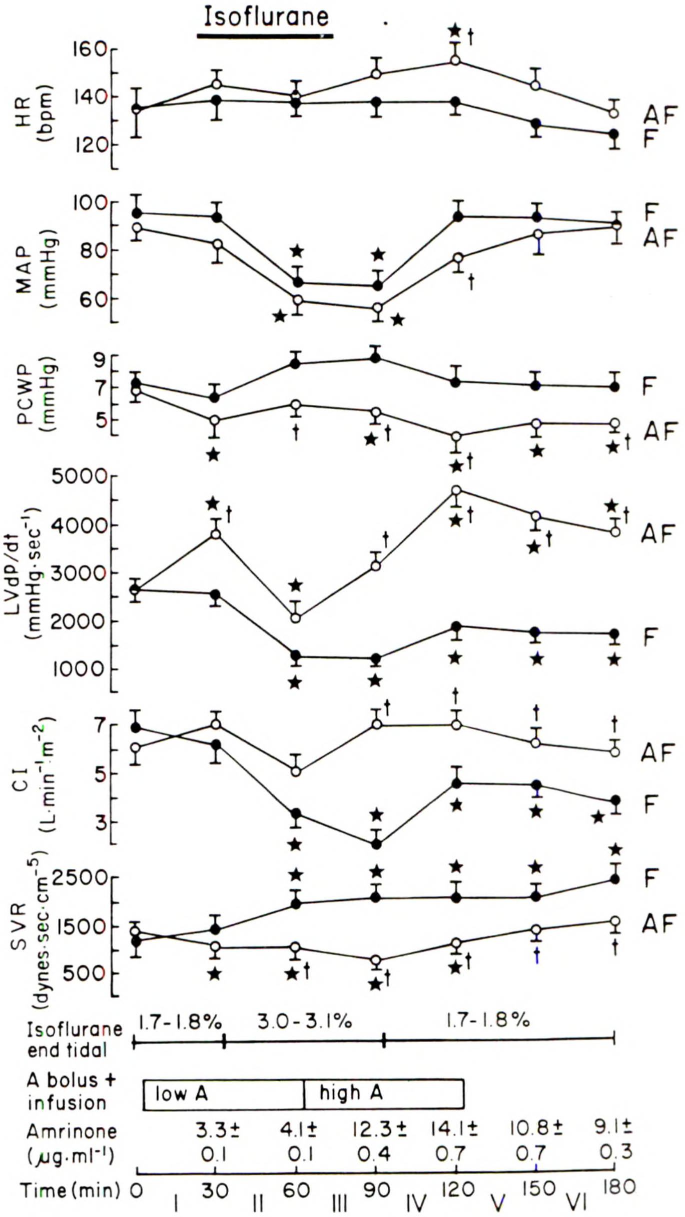

Figure 2. Hemodynamic measurements in the amrinone-isoflurane (AF) group (○), and in the isoflurane (F) alone group (●). Data are expressed as mean ± SEM. Symbols: $^*P < 0.05$ compared to time 0. $^†P < 0.05$ compared to the isoflurane alone group. Low A and high A are the two different successive bolus and infusion rates of amrinone. Amrinone plasma levels shown are expressed as mean ± SEM (see text).

VI. Blood samples for measurements of serum levels of potassium, sodium, calcium, chloride, and glucose were taken three times during each experiment: at baseline (time 0), 90 min after baseline measurements, and at the time of the final measurements.

Changes with time in each group were analyzed by analysis of variance for repeated measures. The Bonferroni modified *t*-tests were used when analysis of variance for repeated measures indicated significant differences. A nonpaired *t*-test was used to compare group AE to group E and group AF to group F. A *P* value less than 0.05 was considered statistically significant.

Results

There were no differences in any variable at the time of the baseline (time 0) measurements between AE and E or AF and F, or between the 25- and 30-min

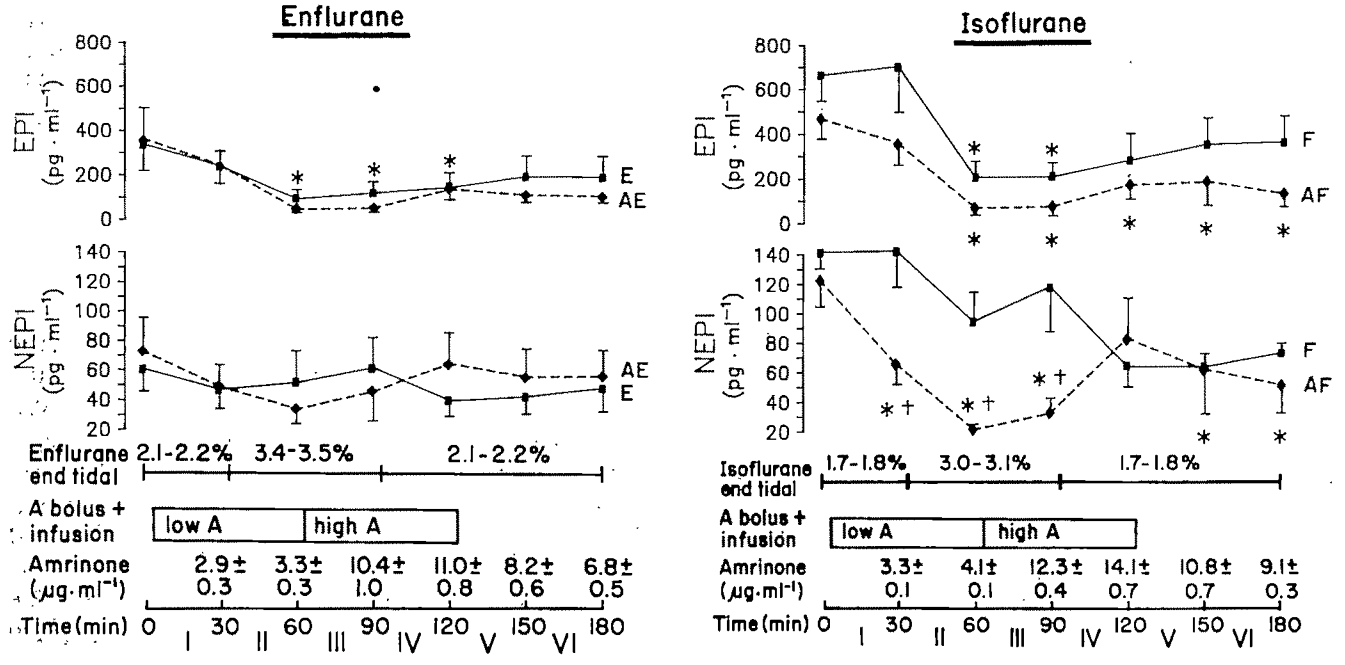

Figure 3. Epinephrine (EPI) and norepinephrine (NEPI) values in the amrinone–enflurane (AE) and in the amrinone–isoflurane (AF) groups (♦—♦), and in the enflurane (E) and isoflurane (F) alone groups (■—■). Data are expressed as mean ± SEM. Symbols: *$P < 0.05$ compared to time 0. †$P < 0.05$ when groups AE or AF were compared to groups E or F respectively. Low A and high A are the two different successive bolus and infusion rates of amrinone. Amrinone plasma levels shown are expressed as mean ± SEM (see text).

values for any variable in any group for any of the measurement periods. There were no differences among the low end-tidal anesthetic concentrations for periods I, IV, V, and VI or the high end-tidal anesthetic concentration for periods II and III for either anesthetic. There were no significant changes caused by the amrinone solvent alone in group E. There were no differences between the mean amrinone plasma levels at the middle and end of each 60-min amrinone infusion with either anesthetic (period I = II; period III = IV). Baseline (time 0) and successive 30-min values for HR, MAP, PCWP, LVdP/dt$_{max}$, CI, and SVR for groups AE and E, and for groups AF and F are given in Figures 1 and 2 respectively. End-tidal concentrations of enflurane or isoflurane, and plasma concentrations of amrinone are given in each figure. Plasma catecholamine levels are shown in Figure 3.

Anesthetic Alone

In groups E and F, compared to low enflurane or low isoflurane, high enflurane or isoflurane significantly depressed cardiac function (Figs. 1 and 2). High enflurane decreased the mean LVdP/dt$_{max}$ from 1550 ± 114 to 890 ± 56 mm Hg/sec; CI from 4.3 ± 0.5 to 2.5 ± 0.3 L·min^{-1}·m^{-2}; and MAP from 85 ± 5 to 67 ± 3 mm Hg. In addition, high enflurane elevated CVP from 4 ± 1 to 7 ± 1 mm Hg and PCWP from 6 ± 1 to 9 ± 1 mm Hg. High isoflurane decreased the mean LVdP/dt$_{max}$ from 2495 ± 167 to 1250 ± 127 mm Hg/sec; CI from 6.0 ± 0.6 to 3.2 ± 0.6 L·min^{-1}·m^{-2}; and MAP from 93 ± 4 to 67 ± 4 mm Hg (period II). These changes returned towards baseline values when enflurane or isoflurane was later reduced (period IV), but never reached baseline levels in the case of CI or LVdP/dt$_{max}$. No changes were observed in HR, PR interval, or PVR compared to time 0 during the changes in concentration for either enflurane or isoflurane.

Anesthetic plus Amrinone vs Anesthetic Alone

Period I: Low Anesthetic, Low Amrinone. Comparisons were made between the values observed in groups AE or AF to the values for low anesthetic alone in groups E or F. At the low enflurane concentration, low amrinone (2.9 ± 0.3 µg/ml) resulted in an increased LVdP/dt$_{max}$ (2460 ± 233 vs 1550 ± 114 mm Hg/sec) and increased HR (141 ± 4 vs 122 ± 5 beats/min). At the low isoflurane concentration, low amrinone (3.3 ± 0.1 µg/ml) increased LVdP/dt$_{max}$ (3715 ± 256 vs 2495 ± 167 mm Hg/sec).

Period II: High Anesthetic, Low Amrinone. At the time of this measurement the amrinone plasma concentrations were 3.3 ± 0.3 µg/ml in AE, and 4.1 ± 0.1 µg/ml in AF. These lower levels of amrinone significantly blunted the decreases in $LVdP/dt_{max}$ and CI that were caused by the high enflurane alone (1360 ± 88 vs 890 ± 56 mm Hg/sec and 4.2 ± 0.4 vs 2.5 ± 0.3 L·min^{-1}·m^{-2}, respectively). However, low levels of amrinone did not block the decreases in cardiovascular function caused by high isoflurane concentrations.

Period III: High Anesthetic, High Amrinone. Amrinone plasma concentrations at the time of measurement in period III were 10.4 ± 1.0 μg/ml in AE, and 12.3 ± 0.4 μg/ml in AF. At high enflurane concentrations, high amrinone caused a statistically significant vasodilation with reduced SVR (1111 ± 127 vs 2408 ± 256 dynes·sec·cm^{-5}); increased $LVdP/dt_{max}$ (1960 ± 166 vs 830 ± 53 mm Hg/sec) and CI (5.3 ± 0.6 vs 2.1 ± 0.2 L·min^{-1}·m^{-2}); and decreased CVP and PCWP (3 ± 1 vs 8 ± 1 mm Hg and 5 ± 1 vs 9 ± 1 mm Hg, respectively). In addition, in the AE group HR was faster (141 ± 3 vs 122 ± 4 beats/min), PR interval was shorter (97 ± 7 vs 113 ± 8 msec), and LVSWI was greater (28 ± 3 vs 13 ± 3 g·m·m^{-2}) than high enflurane alone. However, with low SVR, MAP was the same with high amrinone plus high enflurane as in the high enflurane-only group (61 ± 2 vs 61 ± 4 mm Hg). The findings were similar in the isoflurane groups for period III. In group AF compared to group F, SVR was lower (736 ± 105 vs 2015 ± 162 dynes·sec·cm^{-5}); $LVdP/dt_{max}$ and CI were higher (3145 ± 318 vs 1145 ± 113 mm Hg/sec and 6.9 ± 0.6 vs 2.8 ± 1.3 L·min^{-1}·m^{-2}, respectively); and CVP and PCWP were lower (3 ± 1 vs 5 ± 1 mm Hg and 6 ± 1 vs 9 ± 1 mm Hg, respectively). Also in AF compared to F, HR was faster (149 ± 5 vs 136 ± 4 beats/min) and LVSWI was greater (31 ± 2 vs 16 ± 3 g·m·m^{-2}). However, with low SVR, MAP was the same with high amrinone plus high isoflurane as in the high isoflurane only group (56 ± 3 vs 65 ± 4 mm Hg). Pulmonary vascular resistance was significantly reduced only with high amrinone during high anesthetic (Period III: 90 ± 9 vs 167 ± 28 dynes·sec·cm^{-5} for AE vs E, and 100 ± 13 vs 154 ± 13 dynes·sec·cm^{-5} for AF vs F).

Period IV: Low Anesthetic, High Amrinone. The high amrinone plasma concentrations at this point were 11.0 ± 0.8 μg/ml in AE, and 14.1 ± 0.7 μg/ml in AF. When high enflurane was reduced to low enflurane, compared to group E, group AE had a higher $LVdP/dt_{max}$, CI, and HR (2850 ± 267 vs 1260 ± 102 mm Hg/sec; 5.3 ± 0.7 vs 3.4 ± 0.3 L·min^{-1}·m^{-2}; and 148 ± 3 vs 115 ± 6 beats/min, respectively), and a lower CVP and PCWP (2 ± 1 vs 5 ± 1 mm Hg, and 4 ± 1 vs 8 ± 1 mm Hg respectively). The findings for period IV were similar when high isoflurane was reduced to low isoflurane. Compared to group F, group AF had a higher $LVdP/dt_{max}$, CI, and HR (4720 ± 225 vs 1805 ± 122 mm Hg/sec; 6.9 ± 0.7 vs 4.4 ± 0.5 L·min^{-1}·m^{-2}; and 156 ± 4 vs 137 ± 2 beats/min, respectively), and a lower PCWP (4 ± 1 vs 7 ± 1 mm Hg). However, at this time MAP in group AF was below that of group F (78 ± 3 vs 94 ± 4 mm Hg).

Period VI: Low Anesthetic, Amrinone Infusion Off. Sixty minutes after cessation of the amrinone infusions the amrinone plasma concentrations were still 6.8 ± 0.5 μg/ml in AE, and 9.1 ± 0.3 μg/ml in AF. In AE, PCWP was still lower (4 ± 1 vs 6 ± 1 mm Hg) and $LVdP/dt_{max}$ still higher (2320 ± 189 vs 1240 ± 116 mm Hg/sec) compared to group E. In group AF compared to group F, PCWP was still lower (5 ± 1 vs 7 ± 1 mm Hg) and $LVdP/dt_{max}$ still higher (3780 ± 176 vs 1655 ± 133 mm Hg/sec), and in addition, CI was still higher (5.6 ± 0.5 vs 3.6 ± 0.4 L·min^{-1}·m^{-2} and SVR lower (1480 ± 144 vs 2332 ± 287 dynes·sec·cm^{-5}) in AF.

No arrhythmias were observed at any time in this study. EPI decreased with high enflurane or isoflurane alone. Amrinone did not raise EPI or NEPI levels with either anesthetic; NEPI was reduced in group AF compared to group F during periods I–III (Fig. 3). In all dogs serum electrolytes (potassium, sodium, calcium, and chloride), glucose, and hematocrit were all within normal limits throughout the study.

Discussion

The dose-dependent myocardial depressant effects of inhalation agents in this study are consistent with those of other canine and human studies (8–11,14). Although we did not perform MAC studies in these animals, our low anesthetic concentrations closely approximate previously published values for the MAC of enflurane and isoflurane in dogs (15,16). Even at high concentrations of enflurane or isoflurane that caused marked cardiac depression, sufficient concentrations of amrinone could blunt the deleterious effects of enflurane or isoflurane on myocardial function, reduce SVR and PCWP, restore $LVdP/dt_{max}$, and maintain CI. However, with reduced SVR, MAP remained low. Lowered blood pressure may limit the use of amrinone in patients with severe hypotension or with critical or near critical coronary artery disease. In regard to myocardial metabolic balance, whether reduced perfusion pressure may be outweighed by improved cardiac index, along with reduced cardiac afterload and reduced ventricular wall tension from a reduced preload, cannot be determined from this study.

In addition, another caveat would be that at lower enflurane or isoflurane concentrations, the high amrinone concentrations in this study elevated LVdP/dt$_{max}$ and HR above baseline values. Thus, in the nonfailing heart, excessive amrinone, similar to excessive catecholamine doses, may be deleterious if myocardial oxygen supply is limited. Amrinone has proven clinically useful in the treatment of cardiac failure secondary to ischemic heart disease where presumably decreased ventricular wall tension and decreased afterload offset increases in contractility to result in a decrease in $M\dot{V}O_2$ (17).

The potent inhalation anesthetics are known to alter intracellular calcium homeostasis and have been shown to interfere with slow calcium channel function as well. (18–20) Amrinone inhibits phosphodiesterase, the enzyme responsible for the degradation of cyclic AMP. Increased intracellular cyclic AMP results in an increased number of slow calcium channels in the favorable configuration for calcium influx (21). Increased inward calcium flux appears to be a major mediator of amrinone's ultimate physiologic actions. In addition to these effects on the slow inward current, amrinone has also been demonstrated to alter the pattern of the rate of cardiac muscle relaxation and the ability of sarcoplasmic reticulum to sequester and directly or indirectly release calcium (22). Amrinone could partly counteract the effects of inhalation anesthetics by its positive inotropic action through enhanced Ca^{2+} influx through the slow channels caused by phosphodiesterase inhibition or by other mechanisms.

During these studies no arrhythmias were seen in these previously healthy dogs. There is, at least from the theoretical viewpoint, a risk of arrhythmias with any drug that elevates intracellular levels of cyclic AMP as a part of its mechanism of action (23).This risk may be increased in patients with congestive heart failure because of the high frequency of malignant ventricular arrhythmias in this patient population (24). However during short-term intravenous therapy, the clinical significance of side effects remains controversial (25). Amrinone is not a catecholamine, nor did it cause a vasodilation-induced reflex increase in endogenous circulating catecholamines (Fig. 3). In the present study norepinephrine plasma levels were significantly lower in group AF than in group F after periods I–III; however, it is difficult to say from this experiment whether norepinephrine levels were lower secondary to direct effects of amrinone on components of the autonomic nervous system or on reflex pathways, or whether the norepinephrine levels decreased secondary to improved cardiac function.

In patients with severe congestive heart failure, the density of myocardial β-adrenergic receptors and responsiveness to β-adrenergic agonists may be reduced (26). Potentially, such patients may be relatively more responsive to agents acting distal to the β-adrenergic receptor, and so for these patients the noncatecholamine-mediated cardiotonic properties of amrinone-like drugs may be more suitable than the actions of sympathomimetic amines (27).

The results of this study, showing that amrinone improved cardiac function depressed acutely by two levels of enflurane or isoflurane, suggest that in selected patients amrinone may be beneficial in the short-term treatment of perioperative depression of cardiac performance.

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Halothane Hepatotoxicity in Guinea Pigs

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LIND RC, GANDOLFI AJ, BROWN BR, HALL P DE LA M. Halothane Hepatotoxicity in Guinea Pigs. Anesth Analg 1987;66:222–8.

A recently reported animal model of halothane-associated hepatotoxicity in males of a colored strain of guinea pig was further characterized as to possible sex and strain specificity in outbred albino Amana, inbred albino Hartley, inbred colored strain 2, and inbred colored strain 13 guinea pigs. Exposure to 1% halothane for 4 hr in 21% O_2 proved to be hepatotoxic in both sexes. Forty-eight hours after halothane exposure fatty vacuolization of hepatocytes was present in all animals. Histologically identifiable hepatic necrosis occurred in 60% of the guinea pigs exposed, along with concomitant increases in SGPT. Approximately one half of these responding animals had extensive centrilobular necrosis, which was still present 96 hr after halothane exposure. Females of the inbred strain 2 and males and females of strain 13 were the most susceptible to halothane-induced hepatic necrosis whereas the inbred Hartley strain was almost totally refractory to necrosis. Outbred Amana and male inbred strain 2 animals exhibited an intermediate hepatotoxic response. Comparison of the halothane-associated hepatic lesion with that induced by anoxic/ischemic mechanisms, (exposure to low (8%) oxygen during 1.7% enflurane anesthesia) showed obvious differences in the morphology of the hepatic necrosis and the apparent time course of lesion development. This guinea pig model of halothane-associated hepatotoxicity appears to be superior to previous animal models in that no pretreatment of the guinea pigs is required, both sexes are affected, and the resulting hepatic lesion is more persistent.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane. LIVER—hepatotoxicity.

Previous animal models of halothane-associated hepatic injury have used male rats and required extensive pretreatments and manipulations in order to produce hepatotoxicity: hepatic enzyme induction (1,2), fasting (3), triiodothyronine pretreatment (4), and varying degrees of hypoxia during exposure (2,3,5). Such manipulations have led to questions not only about the mechanisms of toxicity involved (5–8), but also the relevance of the models to the human situation of halothane-associated hepatic dysfunction (9).

Recently, Lunam et al. reported an animal model of halothane hepatotoxicity in males of a colored strain of guinea pig (10). This model requires no treatment prior to a 4 hr exposure to 1% halothane and permits oxygen concentrations during exposure ranging from ambient (21% O_2) to hyperoxic (80% O_2) conditions. In addition, liver necrosis was not present until 48 hr after exposure, with approximately one third of the treated animals developing significant centrilobular necrosis (10). Because only male guinea pigs of a single strain were evaluated, we have undertaken further characterization of this model with regard to sex and strain specificity. The resulting hepatic lesion has been evaluated for the chronology of its development and has also been compared to hepatic necrosis produced by anoxic/ischemic mechanisms (6).

Methods

Male and female guinea pigs of the albino outbred Amana and inbred Hartley strains and colored inbred strains 2 and 13, all weighing 400–700 g, were obtained from a long established colony at the University of Arizona. All animals were housed in stainless steel cages and maintained on a 12 hr light/dark cycle at a room temperature of 22°C. Food and water were provided ad libitum. Their diet was also supplemented with fresh cabbage three times a week.

The guinea pigs were anesthetized in groups of 6–10 animals with 1% (v/v) halothane (Ayerst Laboratories, New York, NY) for 4 hr in a 180 L plexiglass exposure chamber equipped with a circulating fan. The anesthetic was delivered at a flow rate of 6 L/min via a Vernitrol vaporizer (Ohio Medical Products,

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Madison, WI). The oxygen concentration was maintained at 21% O_2 (balance N_2) and monitored with a polarographic oxygen electrode. Anesthetic concentration was checked at regular intervals by gas chromatography. To help maintain body temperature during anesthesia the animals were warmed by two 20-W heaters attached to the underside of the metal plate that served as the floor of the exposure chamber. Body temperatures were monitored using rectal probes attached to a telethermometer (Yellow Springs Instruments, Yellow Springs, OH) and were decreased only 1.5–3.5°C during the 4 hr exposure period. Control animals ($n = 9$) were untreated and included males and females from the Amana, Hartley, and strain 13 strains.

Forty-eight hours after the end of the anesthetic exposure the animals were killed by cervical dislocation while under deep ether anesthesia. Blood was drawn from the inferior vena cava at the juncture with the hepatic vein and subsequently centrifuged to obtain serum. Serum glutamate pyruvate transaminase (SGPT) levels were determined (Sigma Technical Bulletin No. 55-UV; Sigma Chemical Company, St. Louis, MO) and expressed in Wroblewski-LaDue (W-L) units. SGPT in control animals ($n = 9$) was 22 ± 5 U/ml, $\bar{X} \pm$ SD; the range was 17–31. SGPT values greater than 35 U/ml were considered above the normal range.

Sections of hepatic tissue were prepared for histopathologic evaluation by fixation in 10% phosphate buffered formalin followed by processing into 5 μm thick paraffin sections that were stained with hematoxylin and eosin. In order to detect the presence of fat vacuoles within hepatocytes, fixed hepatic tissue was placed in a solution of equal parts 5% potassium dichromate and 1% osmium tetroxide for 6 hr before further processing (11).

Evaluation of the chronology of development and resolution of the hepatic lesion was carried out by exposing separate groups of male and female Hartley and strain 13 guinea pigs to halothane under conditions of the model and subsequently killing them at 0, 6, 12, 24, 48, 72, and 96 hr, as well as 7 days after exposure. At each time point four animals were killed, two Hartley and two strain 13 animals. Selection of these two strains in evaluating the time course was based on initial studies of halothane-induced hepatotoxicity 48 hr after exposure. Strain 13 guinea pigs developed significant levels of hepatic necrosis, whereas the inbred Hartley strain developed only minor hepatic changes after halothane exposure. Thus the time course of both mild and severe hepatic injury could be evaluated. Again, both serum samples and hepatic tissue sections were collected from each animal.

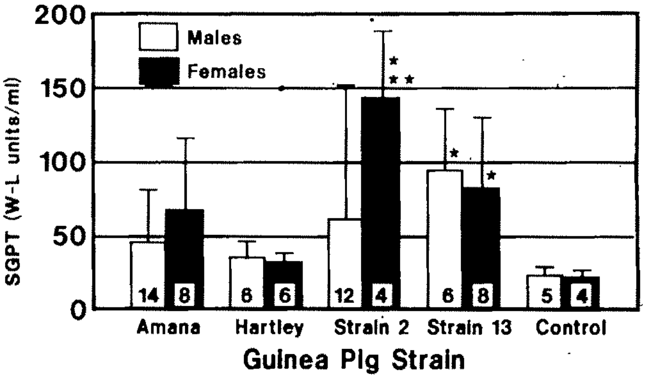

Figure 1. SGPT levels 48 hr after halothane exposure in both sexes of four strains of guinea pig. *$P < 0.05$ vs control values for the same sex. **$P < 0.05$ vs other sex of the same strain. n values in bars.

Sera collected during the time course experiments were also used for measurement of inorganic fluoride ion content as an indicator of the reductive metabolism of halothane that occurred during exposure. Measurement of serum inorganic fluoride was done with Orion selective ion electrodes (Orion Research, Cambridge, MA).

The morphology of the halothane-associated lesion was compared with hepatic necrosis produced by anoxic/ischemic mechanisms. In order to produce anoxic/ischemic hepatic injury, a group of guinea pigs ($n = 10$, composed of five female Amana and five female strain 13 animals) was exposed to 1.7% enflurane (Ohio Medical Products, Madison, WI) for 4 hr at an oxygen concentration of 8% O_2 while being warmed to help maintain body temperature, conditions similar to those previously shown to cause anoxia-related hepatotoxicity in rats (6). One-half the animals were killed immediately after exposure to observe any immediate effects of the enflurane exposure; the other half were killed 48 hr later to allow comparison of the anoxic/ischemic-related hepatic lesion to necrosis induced by halothane exposure.

All values are reported as the $\bar{X} \pm$ SD with statistical analyses made using analysis of variance (ANOVA) with a Newman–Keuls multiple comparison procedure or a one-tailed Student's t-test when applicable. Due to increasing standard deviations with increasing means, the log of SGPT values was used for analysis (12).

Results

Guinea pigs were used in experiments as they were made available from the breeding colony, leading to wide variations in the numbers of animals in each group evaluated (Fig. 1, Table 1).

Table 1. Percentage of Guinea Pig Strains/Sexes with Hepatic Necrosis 48 Hours after Halothane Exposure[a]

			Percent responding[b]		
Strain	Sex	*n*	Mild to moderate[c]	Severe[d]	Total[e]
Amana	M	14	57	14	71
	F	8	13	37	50
Hartley	M	6	50	0	50
	F	6	0	0	0
Strain 2	M	12	42	8	50
	F	4	0	100	100
Strain 13	M	6	33	50	83
	F	8	37	50	87
Total		64	34	27	61

[a] 1% Halothane, 4 hr, 21% O_2.

[b] From histopathologic evaluation of blinded H&E-stained hepatic tissue slides 48 hr after halothane exposure.

[c] Histopathology ranging from scattered foci of necrosis to limited areas of centrilobular necrosis.

[d] Extensive centrilobular necrosis.

[e] Total percentage of animals displaying hepatic necrosis.

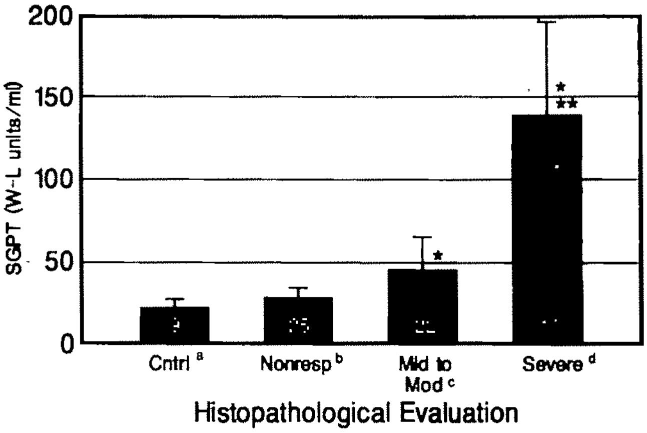

Figure 2. Comparison of histopathologic evaluation with SGPT levels 48 hr after halothane exposure. [a]Control, untreated animals; [b]Nonresponding, histopathologic analysis demonstrated no liver necrosis; [c]Mild to moderate, histopathology ranging from scattered foci of necrosis to limited areas of centrilobular necrosis; [d]severe, extensive centrilobular necrosis. $^*P < 0.05$ vs both control and nonresponding values. $^{**}P < 0.05$ vs mild to moderate values. *n* values in bars.

Blind histopathologic evaluation (Fig. 2) of coded slides by a pathologist (P.H.) revealed distinct levels of hepatotoxic response at 48 hr after exposure that allowed classification of halothane-exposed animals into 3 groups: nonresponsive animals exhibiting no hepatic necrosis; a mild to moderate response that ranged from scattered small foci of necrosis to minor limited centrilobular necrosis (Fig. 3); and a "severe" response that involved extensive centrilobular necrosis (Fig. 4). The SGPT values in each of these three groupings proved to be significantly different from one another, while elevations in SGPT in the mild to moderate and severe responding groups were significantly different from control values (Fig. 2).

Both male and female guinea pigs from the Amana strain and strains 2 and 13 developed varying degrees of hepatic injury 48 hr after exposure to halothane, with members of each group displaying "severe" hepatic necrosis (Fig. 1, Table 1). None of the female inbred Hartley guinea pigs had any evidence of hepatic injury after halothane exposure (Fig. 1, Table 1). The male inbred Hartley strain showed little hepatotoxic response to halothane exposure with three of six animals exhibiting a few scattered foci of necrosis and only a slight, nonsignificant elevation in SGPT at 48 hr (Fig. 1, Table 1). Female inbred strain 2 guinea pigs and both males and females of the inbred strain 13 proved to be the most sensitive to hepatic damage after halothane exposure; all four female strain 2 and one-half of the strain 13 animals developed severe hepatic necrosis (Table 1). These three groups also had the highest 48 hr SGPT levels among the exposed animals with values significantly greater than those in untreated control animals (i.e. control SGPT in males = 23 ± 6 U/ml, $n = 5$; in females = 21 ± 5 U/ml, $n = 4$) (Fig. 1). Unfortunately, because of problems with the availability of female strain 2 animals, only four could be evaluated, which casts doubt on the significance of the degree of their response. Although individual members of both sexes of Amana guinea pigs and male strain 2 animals developed severe hepatic necrosis (Table 1) with fivefold to tenfold elevations in SGPT levels, the wide variation in hepatotoxic response within these groups prevented significant differences from control SGPT values (Fig. 1). Only strain 2 animals had different hepatotoxic responses in males and females, with males having significantly lower 48 hr SGPT values and a lesser incidence of hepatic necrosis than females. (Fig. 1, Table 1).

Monitoring the degree of reductive biotransformation of halothane by measurement of plasma inorganic fluoride levels showed no correlation between serum fluoride level and animals of either strain (inbred Hartley, inbred strain 13) or between sexes. Serum fluoride levels were elevated to 3–8 μM (5.4 ± 2.0 μM, $n = 4$) above background levels immediately after halothane exposure and were 6.8 ± 2.3 μM 6 hr later. These values returned to background levels within 24 hr.

Immediately after halothane exposure, the liver was morphologically normal. In evaluating the time course of development of halothane associated hepatic damage, a single salient feature was noted common to all

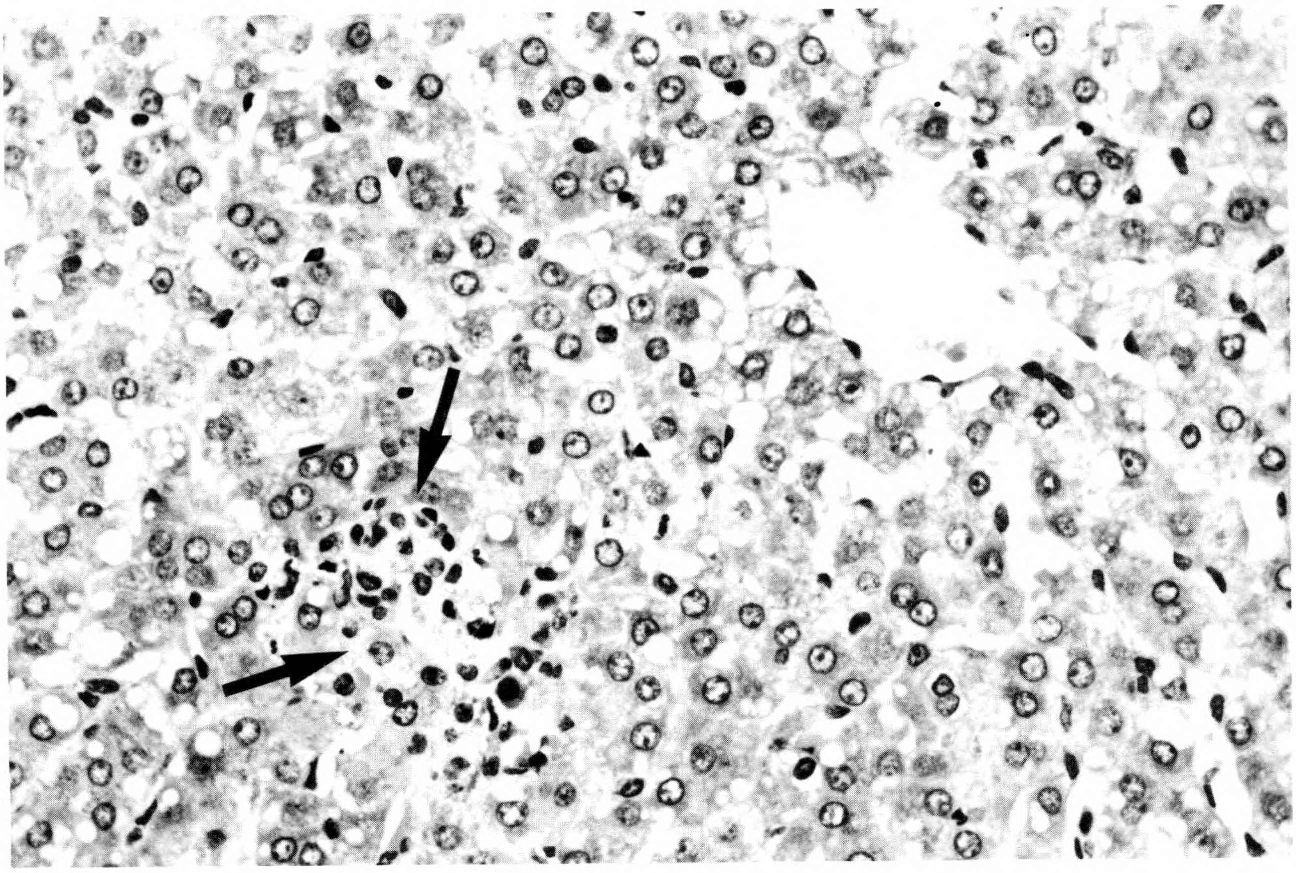

Figure 3. Mild hepatic injury in the form of focal hepatocyte necrosis (arrows) seen in the liver lobules of a female Amana guinea pig 48 hr after exposure to 1% halothane, 21% O_2 for 4 hr. Fatty vacuolization of hepatocytes is also evident (H&E × 400).

exposed guinea pigs: fatty vacuolization of hepatocytes identified by an osmium tetroxide stain. Developing fat vacuoles were found within hepatocytes 6 hr after exposure. By 24 hr the severity of fatty vacuolization ranged from a few tiny droplets in centrilobular cells to extensive vacuolization of nearly all hepatocytes (Figs. 3,4). Fat vacuoles were still present within hepatocytes 7 days after halothane exposure. Although all guinea pigs with severe necrosis had extensive fatty vacuolization, one third of the nonresponding animals that had no necrosis 48 hr after halothane exposure had extensive fatty vacuolization of hepatocytes. Thus the presence of fat droplets was not considered indicative of the degree of hepatic necrosis.

In the guinea pig strain (strain 13) that tended to develop severe necrosis, only the evolution of fatty vacuolization of hepatocytes was found up to 24 hr after halothane exposure. At 24 hr SGPT levels were not elevated, but an occasional degenerating hepatocyte was seen. At 48 hr after halothane exposure, extensive centrilobular necrosis was present with an associated infiltration of inflammatory cells composed primarily of lymphocytes and a few neutrophil polymorphs (Fig. 4). Increasing numbers of inflammatory cells were apparent in the necrotic areas at 96 hr with SGPT levels remaining elevated above 100 U/ml. By 7 days after exposure SGPT values had returned to normal accompanied by resolution of most areas of necrosis.

As opposed to animals developing severe necrosis, the mildly responding animals developed scattered foci of necrosis between 12 and 24 hr after exposure (Fig. 3), although elevations in SGPT did not exceed the upper limit of normal values (35 W-L U/ml) until 48 hr. Even then, SGPT levels were less than 60 U/ml. The foci were still present 96 hr after exposure, but were not noted at 7 days.

The hepatic lesion produced by hypoxic/ischemic mechanisms, i.e., low oxygen enflurane exposure, presented a very different appearance and chronology of development than that occurring after halothane exposure. Immediately after enflurane exposure watery vacuolization of centrilobular hepatocytes was

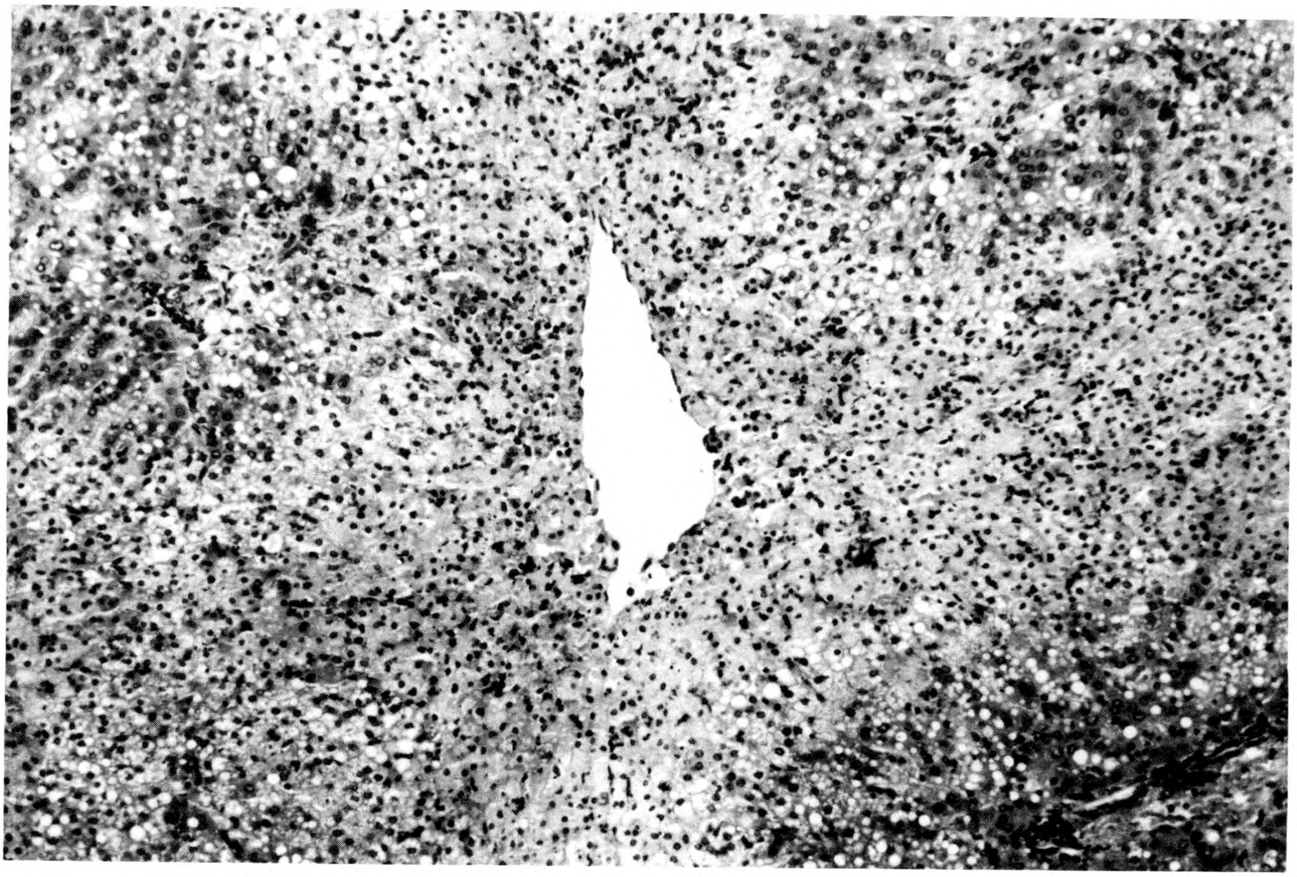

Figure 4. Extensive hepatic centrilobular necrosis seen in a female strain 13 guinea pig 48 hr after exposure to 1% halothane, 21% O_2 for 4 hr. The surviving hepatocytes at the periphery of the liver lobule show fatty vacuolization (H&E × 160).

evident and one of five animals had an SGPT value elevated beyond the normal range (SGPT = 50 U/ml). Liver necrosis 48 hr after enflurane exposure presented itself as distinct areas of coagulative necrosis surrounded by inflammatory cells in three of five animals (SGPT = 32 ± 8 U/ml, n = 5) (Fig. 5). These areas of coagulative necrosis were spotty in occurrence, often subcapsular and panlobular in nature. There was no correlation between the degree of necrosis present and elevation in SGPT levels.

Discussion

Under conditions of the recently reported model of halothane associated hepatic necrosis in males of a colored strain of guinea pig, we found halothane to be hepatotoxic in both sexes of three out of four strains of guinea pig investigated (Fig. 1, Table 1). The degree of necrosis within the liver 48 hr after halothane exposure correlated well with increases in SGPT levels (Fig. 2). Approximately one third of all animals exposed developed extensive centrilobular necrosis (Table 1). This percentage is similar to results obtained by Lunam et al. (10), although three of the groups investigated in the present study had higher percentages of animals with severe hepatic necrosis: inbred strain 2 females (100%); inbred strain 13 males; and strain 13 females (50%) (Table 1). On the other hand, inbred Hartley guinea pigs were almost totally refractory to halothane-induced necrosis. Although the outbred Amana strain and males of the inbred strain 2 included animals that developed severe hepatic necrosis after halothane exposure (Table 1), on the whole they did not have statistically significant elevations in 48 hr SGPT levels (Fig. 1) because of large variations in response within the groups. The reasons for the wide differences in hepatotoxic responses within as well as between groups is unknown at this time, but could provide a valuable tool in future investigations of mechanisms of toxicity. Likewise, caution should be taken to ensure that one possesses either a "responding" or "nonresponding" strain of guinea pig before undertaking biochemical or mechanistic studies.

Reductive biotransformation of halothane by the

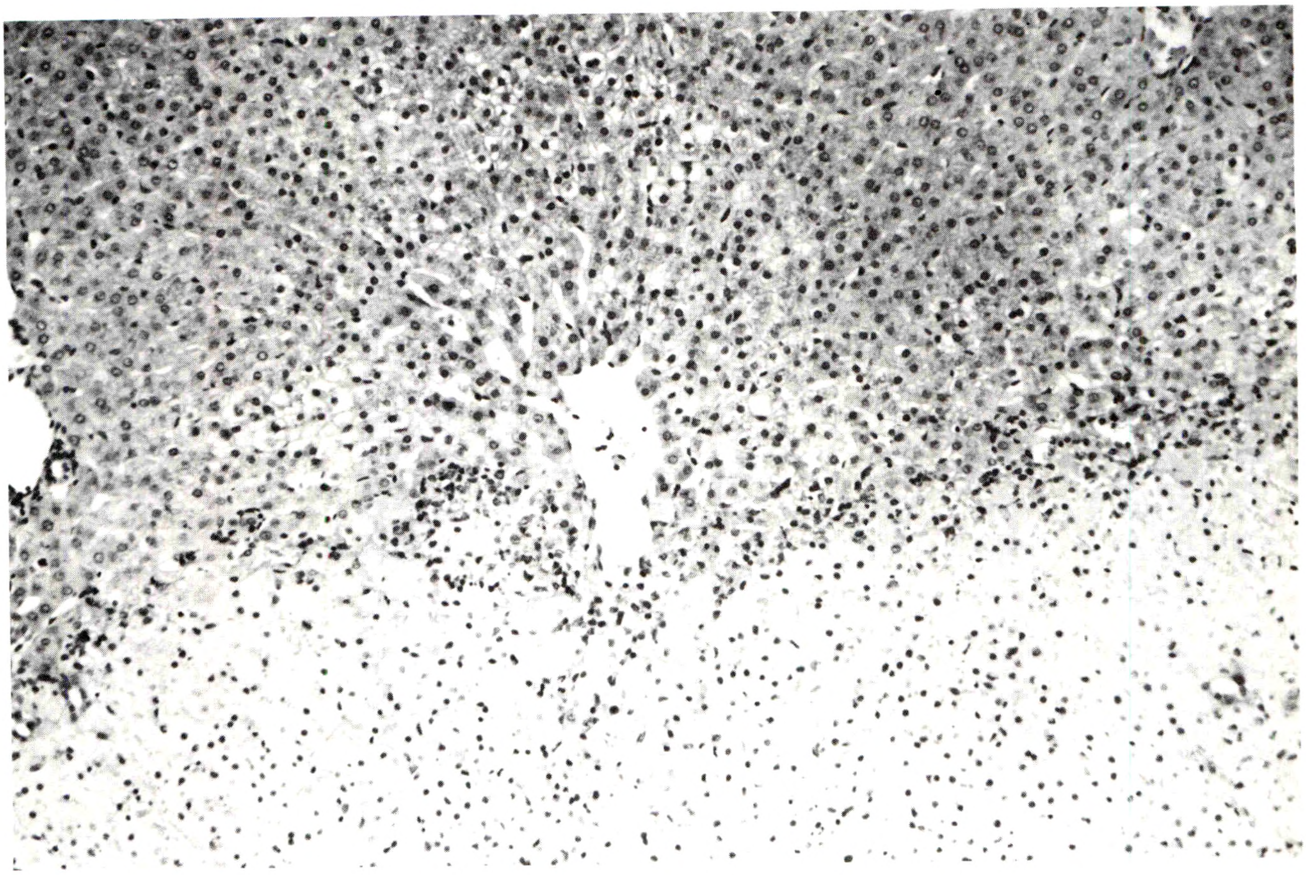

Figure 5. Localized area of hepatic panlobular coagulative necrosis seen in a female Amana guinea pig 48 hr after exposure to 1.7% enflurane, 8% O_2 for 4 hr. A mild inflammatory cell infiltrate is seen at the periphery of the necrotic tissue (H&E × 160).

guinea pigs was evident by the elevated serum inorganic fluoride levels immediately after halothane exposure. Lunam et al. reported excretion of increased amounts of inorganic fluoride in the urine of guinea pigs after halothane exposure with oxygen concentrations as high as 80% O_2 (10). This finding is parallel to the situation of reductive biotransformation of halothane in humans during anesthesia with high oxygen tensions (13,14). It may be that regions of the guinea pig liver are in a hypoxic state during halothane exposure regardless of the concentration of oxygen inspired (15).

In other animal models of halothane-associated hepatic injury, reductive metabolism has been implicated as a possible mechanism of hepatotoxicity (2,7,13). In guinea pigs, no difference was found in serum inorganic fluoride levels after halothane exposure between responding (strain 13) and nonresponding (inbred Hartley) strains. Lunam et al. also failed to show any correlation between the amount of inorganic fluoride excreted in the urine of guinea pigs over 24 hr after halothane exposure and the degree of hepatic necrosis present at 48 hr (10). However, it was demonstrated that inhibition of halothane metabolism during exposure by prior administration of SKF-525A prevented subsequent development of severe necrosis (10). Although it would seem that the degree of reductive biotransformation taking place during halothane exposure is not a factor in the later expression of hepatic necrosis, other aspects of halothane metabolism or cell homeostasis may well be involved.

Although the time course data presented is rather preliminary due to the small numbers of animals evaluated, a distinct difference in both the time course of development and the morphology of the final lesions was seen between the hepatotoxicity induced by halothane exposure or by anoxic/ischemic mechanisms (low oxygen, enflurane exposure). In halothane-exposed animals, the development of extensive centrilobular necrosis with a concomitant increase in SGPT levels did not occur until 24–48 hr after exposure (Fig. 4). SGPT values remained elevated through 96 hr with infiltration of increasing numbers of inflammatory cells into the necrotic areas. The anoxic/ischemic injury, on the other hand, showed watery vacuolization of centrilobular hepatocytes in five of five animals and elevation of SGPT levels in one of five immediately after the exposure period, a response typical of this type of injury (6,16). The lack of a greater hepatotoxic response to the anoxic/ischemic episode may be due to the fact that the animals did not fast overnight before exposure (3,6,17). However, the effect of fasting on the susceptibility to anoxic/ischemic hepatic injury in guinea pigs is not yet known. At 48 hr after enflurane exposure, well developed coagulative hepatic necrosis was present that was spotty in occurrence and panlobular in nature (Fig. 5). This type of necrosis typically develops rapidly after an anoxic/ischemic insult (6,16). These dissimilarities between halothane and anoxic/ischemic-induced hepatic lesions in chronology of evolution and final morphology imply that decidedly different mechanisms of action must be at work.

Although the cellular and molecular mechanisms involved in the production of hepatic necrosis in halothane-exposed guinea pigs remain to be elucidated, this animal model of halothane-associated hepatotoxicity appears to have advantages over previous rat models of the disease. Reductive biotransformation of halothane occurs during anesthetic exposure even under high (80%) oxygen concentrations (10). No pretreatments or extensive manipulations are required to produce hepatic necrosis after halothane exposure. Hepatic damage occurs in both sexes and is more persistent than in rat models (4,18). Fatty vacuolization of hepatocytes develops in all animals exposed. Thus guinea pigs appear to resemble humans more closely than rats do with regard to halothane metabolism (10,13,14) and the acute, mild, hepatic dysfunction associated with clinical halothane anesthesia (19,20).

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Clinical Experience with Adenosine for Controlled Hypotension during Cerebral Aneurysm Surgery

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ÖWALL A, GORDON E, LAGERKRANSER M, LINDQUIST C, RUDEHILL A, SOLLEVI A. Clinical experience with adenosine for controlled hypotension during cerebral aneurysm surgery. Anesth Analg 1987;66:229–34.

The cardiovascular effects of adenosine-induced hypotension were studied in 47 patients undergoing intracranial vascular surgery under neurolept anesthesia. Adenosine infusion (214 ± 18 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased mean arterial pressure (MAP) by 42 ± 1% from 80 ± 1 to 46 ± 1 mm Hg for an average of 29 ± 5 min of hypotension. Hypotension was associated with a minor increase in heart rate (13 ± 2%) and with prolongation of the PR interval (9 ± 2%). ST-T depression did not occur except in one patient with a previous history of myocardial infarction. The adenosine-induced increase in cardiac index (42 ± 9%, $n = 7$) was associated with a 63 ± 10% decrease in systemic vascular resistance index ($n = 7$) while the pulmonary capillary wedge pressure remained unchanged. Adenosine metabolism was limited and there was no accumulation of the end metabolite, uric acid. Serum creatinine levels were normal in all patients postoperatively. We conclude that adenosine rapidly induces a stable and easily controlled hypotension in man without tachyphylaxis or rebound hypertension. There were no signs of renal or myocardial dysfunction except for dysrhythmias that occurred in two patients with a history of myocardial infarction.

Key Words: ANESTHETIC TECHNIQUES—adenosine. ANESTHESIA—neurosurgical.

During the dissection and clipping of cerebral arterial aneurysms, controlled hypotension is often required in order to reduce the aneurysm wall tension, thus minimizing the risk of rupture and bleeding (1). Controlled hypotension is also used to reduce bleeding during other forms of major surgery. Vasodilators such as sodium nitroprusside (SNP) and nitroglycerin (TNG) are currently used for this purpose. However, neither of these are ideal as hypotensive agents; SNP may be associated with side effects such as tachyphylaxis and rebound hypertension (2,3), and TNG has a slow onset and less predictable action. Adenosine is a vasodilator in most vascular beds (4,5) involved in the local regulation of tissue blood flow (6). In dogs, adenosine induces a stable and easily controlled hypotension without signs of tachyphylaxis, effected by a marked reduction of the systemic vascular resistance (7). In a previous clinical study, we used the adenosine uptake inhibitor dipyridamole to minimize the dose requirements of adenosine (8). The present study evaluates the clinical usefulness and side effects of adenosine-induced hypotension in the absence of dipyridamole in a large group of patients undergoing surgery for intracranial aneurysm ligation.

Patients and Methods

Forty-seven patients (20 women and 27 men) were studied, 6–15 days after admission for a subarachnoid hemorrhage (SAH). Forty-six cases were scheduled for intracranial aneurysm surgery and one was operated on for an intracranial arteriovenous malformation. Mean age was 43 ± 2 (SEM) yr (range 21–72 yr). The investigation was approved by the Ethical Committee of the Karolinska Hospital and performed after informed consent had been obtained from the patients.

Two patients had a history of myocardial infarction 9 and 13 yr before the SAH. Two patients had mild arterial hypertension which was treated with β-adrenergic blockers. Forty-three patients had no history of cardiopulmonary disease. Preoperative 12-lead ECG

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was normal in 29 subjects. The two postinfarct patients had ECG signs of earlier myocardial damage. Sinus bradycardia was present in seven patients. Eight patients had minor ST-T abnormalities presumably caused by their SAH, and the ECG in one case showed right bundle branch block.

One hour before operation, the patients were orally premedicated with diazepam, 10–20 mg. Atropine, 0.5 mg, and droperidol, 0.1 mg/kg, were given intravenously before induction. Anesthesia was induced with thiopental, 5 mg/kg, followed by 1–2 mg phenoperidine, a synthetic opiate with longer duration but lower analgesic potency than fentanyl. Pancuronium bromide, 0.1 mg/kg, was given to facilitate tracheal intubation. Anesthesia was maintained with incremental doses of phenoperidine and droperidol when required. Controlled hyperventilation was employed with N_2O in O_2 (F_{IO_2} 0.4) to maintain Pa_{CO_2} values at approximately 3.5 kPa (26 mm Hg). Mannitol, 1–1.5 g/kg, was given routinely at the start of operation. The patients were operated on in the supine horizontal position.

A 1.0-mm plastic cannula was inserted percutaneously into the left radial artery for blood pressure monitoring (MAP) and for blood sampling. In seven patients a balloon-tipped, flow-directed, quadruple-lumen Swan–Ganz® catheter (Model 93A-831-7.5F, VIP) was inserted percutaneously via the left basilic vein, and its correct position in the pulmonary artery was determined by pressure tracings. The catheter was used for the monitoring of central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and for the determination of cardiac output and the infusion of adenosine. In the remaining 40 patients a 1.7-mm catheter was inserted percutaneously via the left basilic vein, and its correct position in the superior vena cava was determined by pressure recordings. The catheter was used for CVP monitoring and infusion of adenosine.

The ECG was monitored with a standard chest (V_5) lead. Heart rate was determined from the R-R interval. The PR interval was also determined, and the position of the ST-T segment was recorded 80 msec after the QRS complex. Blood pressures were recorded via transducers in the midthoracic level. Cardiac output was determined in triplicate according to the thermodilution technique with a cardiac output computer (Edwards Lab. model 9510A). Isotonic glucose, 10 ml at 1°C, was used as thermal indicator. The ECG, heart rate, and blood pressures were continuously recorded on a Grass® polygraph.

Blood gas tensions were measured with appropriate electrodes for pH, P_{CO_2}, and P_{O_2} (Radiometer, Copenhagen). The hemoglobin concentration was determined spectrophotometrically. Samples for the determination of plasma levels of the adenosine metabolites hypoxanthine, xanthine, and uric acid were collected as described by Sollevi et al. (9) and were analyzed in plasma by HPLC according to the method of Schweinsberg and Loo (10). Measurements were made and blood samples obtained immediately before hypotension, as close as possible to the termination of the infusion, and 20–30 min thereafter.

Adenosine (20 mM, 5.3 mg/ml) in isotonic saline was administered by continuous infusion (Critikon roller pump 2102 A) into the superior vena cava during 5–182 min (x = 31.7 ± 4.6 SEM), at a rate of 88–530 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (x = 214 ± 18, corresponding to 15.5 ± 1.5 mg/min). The infusion was started at 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and was increased stepwise by 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 30-sec intervals until the desired MAP level of 40–50 mm Hg was reached. The corresponding volume of infused adenosine solution ranged from 1 to 7 ml/min (x = 2.9 ± 0.3). The total adenosine dose did not exceed 2 g except in one patient who received 6.6 g of adenosine during a 3-hr controlled hypotension.

In all patients serum creatinine levels were determined the day before and the day after surgery. In six patients creatinine clearance was determined the day before and the day after the operation.

Calculations

Body surface area (BSA) was calculated from standard nomograms. Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$) was calculated as cardiac output/BSA. Systemic vascular resistance index (SVRI) was derived from the formula SVRI ($mm\ Hg \cdot L^{-1} \cdot min \cdot m^2$) = (MAP − CVP)/cardiac index, and pulmonary vascular resistance index (PVRI) was derived from the formula PVRI ($mm\ Hg \cdot L^{-1} \cdot min \cdot m^2$) = (PAP − PCWP)/cardiac index.

Statistics

Data are presented as means ± SEM. The statistical significance of comparisons made was determined by Student's *t*-test for paired data. A *P* value of less than 0.05 was regarded as significant.

Results

The induction of controlled hypotension commenced 241 ± 9 min after initiation of anesthesia, during dissection and clipping of the aneurysms. The predetermined MAP level of 40–50 mm Hg was reached within 2.8 ± 0.3 min of adenosine infusion. MAP was

Table 1. Hemodynamic and ECG Variables before, during, and 20–30 min after Adenosine-Induced Hypotension in 47 Patients

	Before adenosine	During adenosine	After adenosine
MAP (mm Hg)	80 ± 1	46 ± 1^b	81 ± 1
Heart rate (beats/min)	60 ± 1	68 ± 2^b	63 ± 2^a
CVP (mm Hg)	4.5 ± 0.4	3.7 ± 0.5^b	4.9 ± 0.4
P-R interval (msec)	161 ± 2	177 ± 5^b	157 ± 5
ST-T depression (mm)	0.4 ± 0.1	0.6 ± 0.1	0.6 ± 0.1

Abbreviations: MAP, mean arterial blood pressure; CVP, central venous pressure.

[a] $P < 0.05$, significantly different from before adenosine values.

[b] $P < 0.01$, significantly different from before adenosine values.

Table 2. Central Hemodynamic Variables before, during, and 20–30 min after Adenosine-Induced Hypotension in 7 Patients

	Before adenosine	During adenosine	After adenosine
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.6 ± 0.2	3.6 ± 0.2^b	2.0 ± 0.3
PAP (mm Hg)	12 ± 1	13 ± 1	13 ± 1
PCWP (mm Hg)	8 ± 1	8 ± 2	7 ± 1
SVRI (mm $Hg \cdot L^{-1} \cdot min \cdot m^2$)	31 ± 3	11 ± 1^b	27 ± 3
PVRI (mm $Hg \cdot L^{-1} \cdot min \cdot m^2$)	1.9 ± 0.4	1.3 ± 0.4^a	2.1 ± 0.4

Abbreviations: PAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

[a] $P < 0.05$, significantly different from before adenosine values.

[b] $P < 0.01$, significantly different from before adenosine values.

reduced by 42 ± 1%, from 80 ± 1 to 46 ± 1 mm Hg (Table 1). Once the desired blood pressure level was reached, MAP was kept constant without adjustments of the infusion rate. The mean hypotensive period lasted 29 ± 5 min. MAP was restored to the prehypotensive levels (Table 1) within 0.5–3 min after the termination of adenosine infusions, except in two patients in whom the prehypotension MAP level was not restored until 10 and 14 min after termination due to arrhythmias (see below). Rebound hypertension did not occur in any of the cases.

Central venous pressure decreased 16 ± 7% (n = 47, Table 1), while no changes in PAP or PCWP were seen in the seven patients with a pulmonary artery catheter (Table 2). Cardiac index increased 42 ± 9% in combination with a 63 ± 4% decrease in SVRI. There was also a reduction in PVRI (39 ± 24%, Table 2).

The influence of adenosine on the blood gas tensions and acid–base balance was small, with pH, base excess, and Pa_{CO_2} unaffected while Pa_{O_2} decreased 12 ± 5% (Table 3). There was a small increase of the adenosine metabolites hypoxanthine and uric acid during the adenosine infusion; however, xanthine levels were unaffected (Table 4). Twenty minutes after the termination of the infusion, hypoxanthine and uric acid levels remained slightly above baseline values. The total dose of adenosine administered did not correlate with the small variation in the metabolite levels (data not shown). The preoperative serum creatinine level was 78 ± 2 μmol/L and the creatinine clearance in six patients was 86 ± 4 ml/min. On the first postoperative day the serum creatinine was 75 ± 2 μmol/L and the creatinine clearance values were within normal values in all cases (88 ± 6 ml/min).

There was a minor but statistically significant increase in heart rate (8 ± 1 beats/min, Table 1). The PR interval increased 9 ± 2% during hypotension. In three patients the PR interval exceeded 210 msec, indicating atrioventricular block type 1. One subject developed junctional rhythm during hypotension. The influence on AV conduction was dose-dependent; however, AV block type 1 or junctional rhythm occurred at variable infusion rates (140–350 $\mu g \cdot kg^{-1} \cdot min^{-1}$). ST-T segments were not affected, except in one of the two patients with previous myocardial infarction. This patient developed ST-T segment depression followed by ventricular tachycardia (for 2 min) approximately 5 min after the induction of hypotension. In this patient, a normal rhythm and ECG were restored after termination of the adenosine infusion and after the IV injection of lidocaine, 75 mg. The incident did not affect the clinical course of the subject and postoperative ECGs and myocardial enzyme determinations showed no evidence of myocardial infarction. The other patient with a previous myocardial infarction developed atrial flutter, which was terminated during hypotension by the administration of IV propranolol (1 mg).

There were two deaths, both postoperative, in this series of patients, but adenosine was not considered to be involved in the fatal outcome in either of these cases. One patient with several cerebral aneurysms had a perioperative aneurysm rupture during the difficult surgical dissection and ligation procedure. The hypotension period lasted for 180 min. This patient was awake without neurologic deficits immediately after surgery, but 8 hr after surgery developed hemiplegia and aphasia, and died on the third postoperative day. Autopsy showed cerebral infarction in the area of distribution of the middle cerebral artery on the operated side. In the second fatal case, the operation and hypotension (11 min) were uneventful. This patient developed a hemiparesis 12 hr after surgery and died on the third postoperative day. Autopsy showed cerebral infarction in the area of the middle cerebral artery on the operated side.

Table 3. Arterial Blood Gases before, during, and 20–30 min after Adenosine-Induced Hypotension in 21 Patients

	Before adenosine	During adenosine	After adenosine
Pa_{O_2}			
kPa	19.7 ± 1.5	17.3 ± 2.0[a]	19.8 ± 1.3
mm Hg	148 ± 11	130 ± 15[a]	149 ± 10
Pa_{CO_2}			
kPa	3.6 ± 0.1	3.6 ± 0.1	3.8 ± 0.1
mm Hg	27 ± 1	27 ± 1	29 ± 1
pH	7.50 ± 0.01	7.47 ± 0.02	7.48 ± 0.01
Base excess (mmol/L)	−0.7 ± 0.4	−1.6 ± 0.7	−1.4 ± 0.6

Values are means ± SEM.

[a] $P < 0.05$, significantly different from before adenosine values.

Table 4. Purine Levels in Arterial Plasma before, during, and 20–30 min after Adenosine-Induced Hypotension in 10 Patients

	Before adenosine	During adenosine	After adenosine
Hypoxanthine (μmol/L)	1.5 ± 0.3	9.8 ± 1.7[b]	3.4 ± 0.6[b]
Xanthine (μmol/L)	4.1 ± 1.9	3.8 ± 1.7	3.6 ± 1.4
Uric acid (μmol/L)	188 ± 28	216 ± 28[a]	210 ± 35[a]

Values are means ± SEM.

[a] $P < 0.05$, significantly different from before adenosine values.

[b] $P < 0.01$, significantly different from before adenosine values.

Discussion

The present study demonstrates that adenosine is an effective agent for controlled hypotension in man. The rapid induction, stable action, and rapid restoration of blood pressure after its termination are in agreement with our first clinical study (8) in which adenosine was used for hypotension after pretreatment with the adenosine uptake inhibitor dipyridamole. In the absence of dipyridamole the mean dose requirement of adenosine increased by 50% from 0.14 to 0.21 $mg \cdot kg^{-1} \cdot min^{-1}$. The clinical solution of adenosine used in the present study had a fourfold greater concentration than in the first study (5.3 vs 1.3 mg/ml), which enabled the induction of profound hypotension with infusion rates of about 100–300 ml per hour. Slightly higher infusion rates were required only in a few young male subjects.

The adenosine-induced hypotension was caused by a profound reduction of the systemic vascular resistance that paralleled an increase in cardiac output (see Table 2) (8). Cardiac filling pressure was virtually unaffected. Thus the enhanced cardiac output during the adenosine infusion can probably be explained by the combination of marked resistance vessel dilatation, maintained venous filling pressure, and maintained myocardial performance. The preferential afterload-reducing effect of adenosine makes it different from other vasodilators used for controlled hypotension (8,11). However, our clinical experience with adenosine-induced hypotension is limited to intravenous anesthesia. The effect of adenosine on central hemodynamics during inhalation anesthesia has not yet been evaluated in man.

Although many peripherally acting hypotensive agents induce significant reflex tachycardia (12), the heart rates in this study increased by only 8 ± 1 beats/min during adenosine hypotension. This limited reflex tachycardia may be explained by different mechanisms. First, it has been demonstrated that high adenosine concentrations in man have an inhibitory influence on sinus node automaticity (13,14). Secondly, adenosine may have a presynaptic inhibitory effect on sympathetic nerves of the myocardium (15). Thirdly, as demonstrated in the dog, sympathoadrenal activation is comparatively minor during adenosine-induced hypotension (see below). Adenosine may also prolong atrioventricular conduction time. This effect has been demonstrated in animal and human studies in which bolus injections of the drug were used (16). With this mode of administration, high doses may even induce transient AV blocks. During the present study there was a small but significant 9% prolongation of the PR interval. In three cases the PR interval indicated AV block type 1. Thus, the present hypotensive infusion rates of adenosine were not associated with severe prolongation of AV conduction. Furthermore, it is our clinical experience that other methods for controlled hypotension such as isoflurane, SNP, and TNG may occasionally be associated with junctional rhythm. However, during simultaneous administration of drugs that counteract adenosine uptake (such as dipyridamole) the effect of adenosine on AV conduction is more potentiated than is the hemodynamic response (17).

The effects of adenosine-induced hypotension on myocardial blood flow has not yet been studied in man. Studies in dogs have demonstrated marked coronary vasodilatory effect of local adenosine administration (18), and increased coronary blood flow with reduced myocardial oxygen demand during adenosine-induced hypotension (19). Circumstances may be different in the clinical situation. In patients with coronary disease, for instance, such as proximal coronary stenosis, vasodilatory drugs may cause regional myocardial ischemia due to redistribution of blood flow away from areas supplied by the stenotic vessel (20). This phenomenon may explain the transient myocardial ischemia seen in one patient with a previous myocardial infarction. Therefore, the indication for controlled hypotension, as well as the optimal blood pressure level should, even with adenosine, be carefully weighed in patients with ischemic heart disease.

Pharmacologically induced hypotension is usually associated with increased sympathetic nervous tone due to activation of baroreceptors (21). In the dog, SNP-induced hypotension is associated with a significant increase in circulating catecholamines, whereas the increase is small during ATP-induced hypotension (22). Similar results were found in the dog when comparing adenosine and sodium nitroprusside (own unpublished data). The similarities between the sympathoadrenal effects of ATP and adenosine are not unexpected because ATP is rapidly degraded to adenosine in the circulating blood (9). Adenosine also differs from SNP with respect to activation of the renin–angiotensin system. Whereas plasma renin activity markedly increases during SNP-induced hypotension in the dog, it is unaffected by adenosine (23). This difference may explain the absence of tachyphylaxis and rebound hypertension in the present study. However, clinical data on plasma catecholamine and renin activity during adenosine-induced hypotension are not yet available.

Exogenous adenosine is mainly eliminated by cellular uptake (4), but adenosine can also be metabolized to uric acid. Uric acid that accumulates to pathologic levels may precipitate in the kidney. A limited increase in uric acid levels (15 ± 5%) was observed in the present study, but in no subject were pathological levels seen. However, to elucidate this question further, investigations on adenosine metabolism during high-dose administration for longer periods (>1 hr) are required. In addition, care should be taken in patients with gout or other conditions of disturbed purine metabolism.

The hypotensive period was not associated with elevations of serum creatinine or reduction in creatinine clearance ($n = 7$) in any patient. This finding is in agreement with our earlier study (8) and offers gross evidence of the maintenance of renal function during adenosine induced hypotension.

The acid–base status was unaffected during an average of 30 min of hypotension. The absence of acidosis is in contrast to studies in dogs where, similar levels of hypotension are associated with decreases in arterial pH (24). This reduction of pH in dog models is probably not explained by lactate formation (7,24), and has not been confirmed in man (8). The difference is not related to the duration of hypotension or type of anesthesia but rather represents species differences.

There was a modest decrease in arterial P_{O_2} that was of no clinical significance in any of the cases. Reduction of arterial P_{O_2} is a well known phenomenon during hypotension induced by other peripheral vasodilators such as SNP and TNG (25), and may be explained by increased venous admixture because of inhibition of hypoxic pulmonary vasoconstriction (26).

In conclusion, adenosine induces a stable and easily controlled hypotension without negative effects on cardiac output or acid–base balance in patients undergoing cerebral aneurysm surgery during neurolept anesthesia. The use of adenosine hypotension should be carefully considered in patients with ischemic heart disease because in this clinical study, dysrhythmias occurred in the two subjects with earlier history of myocardial infarction. Adenosine-induced hypotension should be avoided in patients with disturbed purine metabolism. However, we find adenosine to be a useful alternative as a vasodilator agent for controlled hypotension in man, although additional clinical experience is required concerning its effects on regional blood flow and metabolism.

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Meperidine as a Spinal Anesthetic Agent:
A Comparison with Lidocaine–Glucose

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SANGARLANGKARN S, KLAEWTANONG V, JONGLERTTRAKOOL P, KHANKAEW V. Meperidine as a spinal anesthetic agent: a comparison with lidocaine–glucose. Anesth Analg 1987;66:235–40.

The anesthetic effects of 2 ml of 5% lidocaine in 7.5% glucose (LG) or 5% meperidine in water were evaluated and compared in 40 ASA class 1 or 2 patients. Patients were randomly assigned to one of the two groups (20 patients in each) according to the anesthetic agent, which was injected into the lumbar subarachnoid space in the sitting position. The patients remained sitting for 5 min before being placed in the supine position. Times of onset of sensory and complete motor blockade were significantly more rapid with LG. The extent of maximum cephalad spread of analgesia and the time to maximum height of analgesia in the two groups were not different. Duration of analgesia at the T-7 (48.96 ± 6.64 min with LG, 44.74 ± 6.14 min with meperidine; means ± SEM) and L-1 (94.37 ± 7.42 min with LG, 76.19 ± 5.64 min with meperidine) dermatomes was not different in the two groups but was statistically longer at the T-10 dermatome with LG (66.83 ± 6.72 min) than with meperidine (46.66 ± 6.26 min). The duration of complete motor blockade was also significantly longer with LG (66.44 ± 7.05 min) than with meperidine (42.67 ± 4.47 min). Complications in both groups included decrease in blood pressure and nausea and vomiting intraoperatively, and urinary retention, nausea and vomiting, and mild headache postoperatively. Complications that occurred only in the meperidine group were intraoperative drowsiness, respiratory depression, bronchospasm, and itching. The frequency of complications was greater with meperidine. The number of patients requiring only oral medication for pain relief during the first 24 hr after surgery was significantly greater in the meperidine group but the number of patients who were pain free and required neither oral nor narcotic analgesic did not differ. Meperidine–water as the sole spinal anesthetic agent in this study had no significant advantage over lidocaine–glucose.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—meperidine, lidocaine. ANALGESICS—meperidine.

Meperidine, known to have local anesthetic properties (1), has been used successfully for spinal anesthesia although with a number of complications (2,3). The extent and duration of sensory and motor blockade obtained from intrathecal injection of meperidine in a dose of 1 mg/kg body weight were adequate for surgery on the lower abdomen, perineum, and lower limbs, and postoperative analgesia was prolonged. However, the effectiveness of meperidine for spinal anesthesia has never been compared with a local anesthetic agent. We therefore conducted this study to make a comparison of lidocaine and meperidine for spinal anesthesia.

Methods

Forty ASA class I and II patients between the ages of 15 and 65, without history of drug allergy or narcotic abuse, and scheduled to have surgery of the lower abdomen or lower extremities were assigned randomly to receive either 2 ml of 5% lidocaine in 7.5% glucose (Xylocaine 5% Heavy, Astra) (LG) or 2 ml of 5% meperidine in water (Pethidine Injection BP 1980, The Government Pharmaceutical Organization, Bangkok, Thailand) as the spinal anesthetic agent for surgery. The specific gravity of meperidine measured by total solid meter refractometry (American Optical Corp., Buffalo, NY) was about 1.026. This study was approved by the Hospital Committee for research and written consent was obtained from all the patients.

In the operating room, an intravenous catheter was inserted and 500 ml of 5% lactated Ringer's solution was infused within 20–30 min. Baseline levels of blood pressure and heart rate were recorded. Subarachnoid puncture was performed using a 25-gauge spinal needle

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at the L3-4 or L4-5 interspace with the patient in the sitting position. After either LG or meperidine was injected intrathecally and the spinal needle withdrawn the patient remained sitting for 5 min before being placed in the supine position. Measurements of blood pressure, heart rate, sensory and motor blockade were made every 2 min for the first 10 min after the injection was completed, then every 10–15 min until the sensory blockade declined below the L-1 dermatome.

Measurements of Sensory Blockade

The patients were tested for analgesia to pinprick and the upper and lower limits of segmental analgesia were charted on graph paper. Times to initial onset of analgesia and to maximum spread were determined from the data plotted as described by Bromage (4). Patients who failed to achieve analgesia above the L-1 dermatome within 30 min after the injection were considered spinal block failures and general anesthesia was generally given.

Measurement of Motor Blockade

Motor blockade was determined according to a modified Bromage scale (4): 0 = no paralysis; 1 = inability to raise the extended leg; 2 = inability to flex the knee; 3 = inability to flex the ankle joint. During recovery motor blockade was assessed as follows: 1 = ability to raise extended leg but not flex ankle joint or toes; 2 = ability to flex knee; 3 and 0 are according to the scale above.

Decreases in systolic blood pressure greater than 30% below baseline levels and assumed to be due to sympathetic blockade were treated with infusion of lactated Ringer's solution and with vasopressors. Respiratory depression caused by meperidine was treated with intravenous naloxone. Nausea and vomiting associated with hypotension were treated with oxygen inhalation, intravenous fluid infusion and small doses of vasopressor. If nausea and vomiting persisted after hypotension had been corrected, 10 mg of metoclopramide were given intravenously with, if the patient was in the meperidine group, small doses of naloxone. All patients were followed throughout their hospital stay and all complications were recorded. During the first 24 hr after surgery, the patients were initially treated with 1 g of oral acetaminophen whenever analgesic medications were required. If this was inadequate, analgesic doses of narcotics were used.

In the statistical treatment of the study results, intergroup differences were tested for significance by comparing data by means of a two-tailed Student's *t*-test. The χ^2 test was applied to explain associations between variables. $P < 0.05$ was considered statistically significant. All values are given as means ± SEM.

Table 1. Characteristics of Patient Groups

	Lidocaine–glucose	Meperidine
Type of operation		
Anal	2	3
Orthopedics	6	2
Gynecologic	4	6
Urologic	5	7
Superficial (plastic, tumor)	3	2
Total	20	20
Age[a] (yr)	46.5 ± 3.0	42.8 ± 3.9
Weight[a] (kg)	60.7 ± 3.6	56.6 ± 1.6
Height[a] (cm)	161.0 ± 1.6	159.2 ± 1.7

[a] Mean values ± SEM.

Results

Twenty patients received LG and 20 received meperidine as the spinal anesthetic. In the LG group, ten received no premedication, two received 5 mg diazepam, one received 10 mg diazepam, and seven received 7.5 mg midazolam. The premedications were given orally about 1 hr before surgery. None of the patients in the meperidine group was premedicated. Mean ages, weights, heights, and operations in both groups are shown in Table 1. There were no significant intergroup differences.

Sensory Blockade

One patient in the LG group had inadequate sensory blockade with a level of analgesia at L-5. In the meperidine group, two patients had levels of analgesia at L-4 and S-1. These three patients were excluded from further study.

The time to initial onset of sensory blockade was significantly shorter ($P < 0.01$) in the LG group than in the meperidine group. The cephalad spread of analgesia to the L-1 dermatome was significantly more rapid ($P < 0.05$) in the LG group than in the meperidine group. The maximum cephalad spread of analgesia and the time of maximum spread were not different in the two groups. There was no correlation between age, weight, height, and the maximum cephalad spread of analgesia (Table 2).

No difference was found in caudal spread between the two groups. Initially the meperidine group had less pronounced caudal spread, but by 8–30 min after

Table 2. Latencies and Spread of Sensory Blockade

	Lidocaine–glucose	Meperidine
Time to onset of analgesia (min)[a]	2.4 ± 0.24	4 ± 0.48
Time to spread of analgesia to L-1 (min)[b]	10.74 ± 0.85	17.83 ± 3.10
Time to maximum cephalad level of analgesia (min)	29.37 ± 3.28	34.17 ± 3.71
Segmental maximum level of analgesia	T-7.4 ± 0.5	T-7.2 ± 0.7

Values are mean ± SEM.
[a] Significant between groups ($P < 0.01$).
[b] Significant between groups ($P < 0.05$).

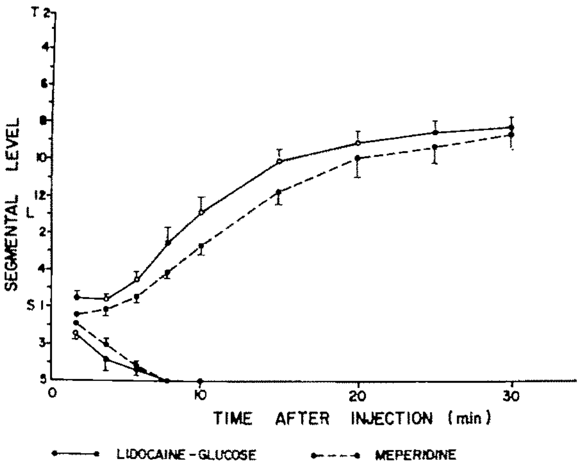

Figure 1. Cephalad and caudal spread of sensory blockade with lidocaine–glucose or meperidine as the spinal anesthetic agent. Data expressed as mean ± SEM.

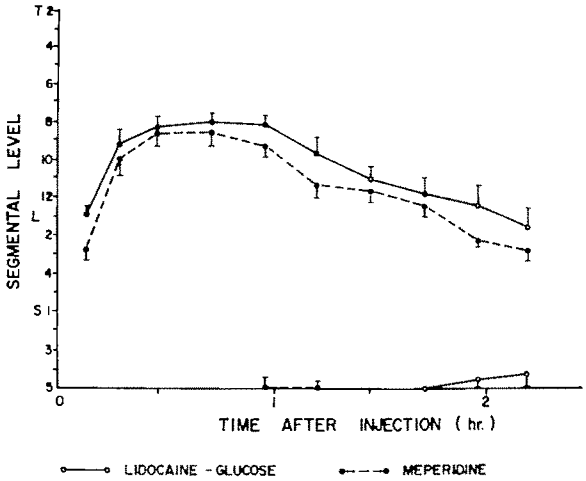

Figure 2. Cephalad and caudal spread of sensory blockade with lidocaine–glucose or meperidine as the spinal anesthetic agent. Data expressed as mean ± SEM.

injection no difference could be found between the two groups (Figs. 1,2).

A two to three segment regression in cephalad spread of sensory blockade was observed after 1 hr in both groups (Fig. 2). Duration of analgesia was significantly longer with LG than with meperidine at the T-10 ($P < 0.05$) but not at the T-7 and L-1 dermatome levels (Table 3, Fig. 3).

Motor Blockade

Complete motor blockade of the lower limbs (degree 3) was seen in 18 patients in the LG group for about 60 min and in 16 patients in the meperidine group for about 40 min. The onset was significantly more rapid ($P < 0.05$) with LG (Table 4, Fig. 4). There was one patient in the meperidine group who developed complete motor blockade after 40 min. A significant difference in duration of degree 2 ($P < 0.05$) and degree 3 ($P < 0.01$) motor blockade was seen between the two groups (Table 5, Fig. 5).

Postoperative Analgesia

Frequency with which postoperative analgesics were needed ranged in both groups from 0 to 4 during the first 24 hr after surgery. The number of patients in whom pain was relieved with oral acetaminophen alone was significantly greater ($P < 0.025$) in the meperidine group (11 patients) than in the LG group (four patients). Three patients in each of the groups required neither oral medication nor narcotic analgesics. The operations performed in these patients were transurethral prostatectomy (one in each group), conization of the cervix (one in the LG group), synovectomy of the knee joint (one in the LG group), anal fistulectomy (one in the meperidine group), and skin grafting on the thigh (one in the meperidine group).

Intraoperative Complications

Decreases in blood pressure of more than 30% below baseline levels were seen in 1 patient who had maximum cephalad spread of analgesia to T-4 in the LG

Table 3. Duration of Analgesia at Different Segmental Levels

Segment	Lidocaine–glucose (min)	n	Meperidine (min)	n
T-7	48.96 ± 6.64	10	44.74 ± 6.14	8
T-10^a	66.83 ± 6.72	17	46.66 ± 6.26	15
L-1	94.37 ± 7.42	19	76.19 ± 5.64	18

Values are mean ± SEM.
^{a}Significant between groups ($P < 0.05$).

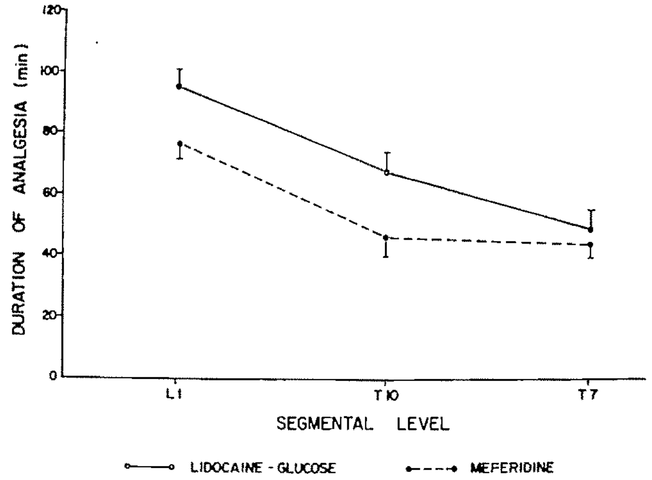

Figure 3. Duration of analgesia at different segmental levels with lidocaine–glucose or meperidine as the spinal anesthetic agent. Data expressed as mean ± SEM.

Table 4. Complete Motor Blockade of the Lower Limbs

	Lidocaine–glucose	Meperidine
Frequency	18/19	16/18
Time to onset^{a,b} (min)	14.39 ± 2.16	21.25 ± 2.31
Duration^{a,c} (min)	66.44 ± 7.05	42.67 ± 4.47

^{a}Mean values ± SEM.
^{b}Significant between groups ($P < 0.05$).
^{c}Significant between groups ($P < 0.01$).

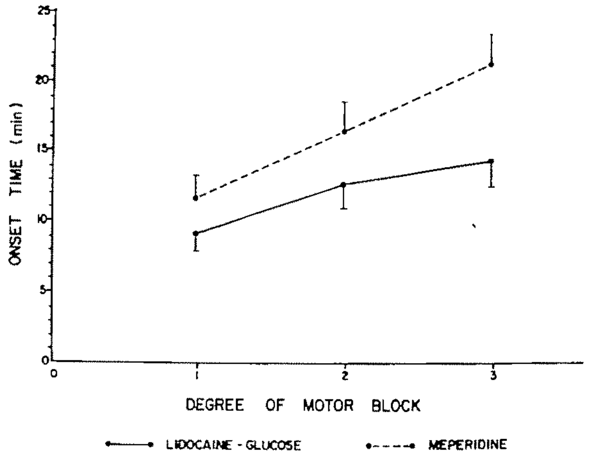

Figure 4. Onset of different degrees of motor blockade with lidocaine–glucose or meperidine as the spinal anesthetic agent. Data expressed as mean ± SEM.

group and in 2 patients, with cephalad spread of analgesia to T-8 in one and T-2 in another, in the meperidine group. They responded well to rapid intravenous fluid infusion and small doses of vasopressors. The incidence of hypotension was not significantly different in the two groups.

Intraoperative nausea and vomiting occurred in 3 patients in the LG group; in one it was associated with a decrease in blood pressure. In the meperidine group nausea and vomiting with severe retching were seen in 11 patients, one of whom also had associated hypotension. The symptoms were not relieved by restoration of blood pressure and oxygen inhalation. All were treated with 10 mg intravenous metoclopramide, an antiemetic with actions on both the gastrointestinal tract and the central nervous system (5,6). In the LG group nausea and vomiting were successfully treated. In the meperidine group nausea and vomiting were completely relieved in seven patients within a few minutes after initiation of treatment, in three patients relief was only partial, and one patient needed 0.04 mg intravenous naloxone to relieve nausea and vomiting. The incidence of intraoperative nausea and vomiting was significantly higher in the meperidine group ($P < 0.005$).

All the patients in the LG group were alert during operation. Fourteen patients in the meperidine group were drowsy and all those who had intraoperative nausea and vomiting became drowsy after the symptoms were relieved. The incidence of intraoperative drowsiness was significantly higher in the meperidine group ($P < 0.0001$). One patient in the meperidine group (female, age 21, weight 44.5 kg, height 146 cm) became stuporous and had irregular slow respiration (rate below 10/min) 18 min after injection of the spinal anesthetic. The cephalad level of analgesia was at the T-2 dermatome when the symptoms began. She was treated with oxygen and intermittent positive pressure ventilation for about 30 min before the symptoms disappeared.

One patient in the meperidine group with cephalad level of analgesia to the T-6 dermatome developed bronchospasm. She had no previous history of asthma. The bronchospasm was improved by subcutaneous injection of 0.5 ml of 1:1000 epinephrine (see Table 6).

Table 5. Duration of Different Degrees of Motor Blockade of the Lower Limbs

Motor block[a]	Lidocaine–glucose (min)	n	Meperidine (min)	n
1	92.03 ± 6.8	19	79.0 ± 6.47	18
2[b]	76.84 ± 7.27	19	56.68 ± 5.65	18
3[c]	66.44 ± 7.05	18	42.67 ± 4.47	16

Values are mean ± SEM.

[a] Degree of motor block based on modified Bromage scale (4) as described in text.

[b] Significant between groups ($P < 0.05$).

[c] Significant between groups ($P < 0.01$).

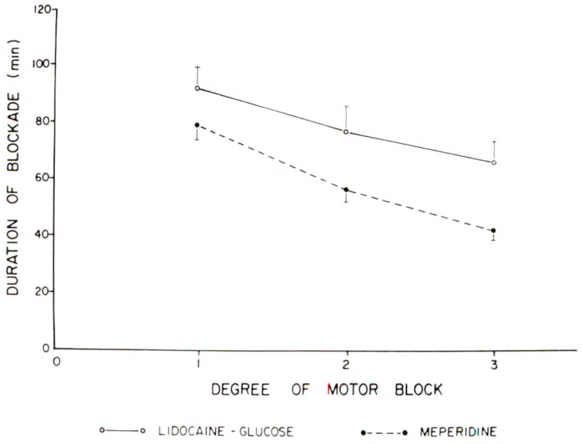

Figure 5. Duration of different degrees of motor blockade with lidocaine–glucose or meperidine as the spinal anesthetic agent. Data expressed as mean ± SEM.

Table 6. Frequency of Complications

	Lidocaine–glucose[a]	Meperidine[b]
Intraoperative		
BP decrease > 30% of control value from sympathetic blockade	1	2
Nausea, vomiting[c]	3	11
Drowsiness[d]	0	14
Respiratory depression	0	1
Bronchospasm	0	1
Postoperative		
Urinary retention[e]	1	6
Mild headache	5	5
Nausea, vomiting	4	6
Itching	0	2

[a] $N = 19$.

[b] $N = 18$.

[c] Significant between groups ($P < 0.005$).

[d] Significant between groups ($P < 0.0001$).

[e] Significant between groups ($P < 0.05$).

Postoperative Complications

Urinary retention on the first postoperative day occurred significantly more frequently in the meperidine group than in the LG group ($P < 0.05$). Urinary catheterization was not needed more than twice during the 24 hr period in any patient. Five patients in each of the groups had mild headache on the first postoperative day. No postspinal headache was seen.

Other complications were postoperative nausea and vomiting. The itching in the two patients in the meperidine group involved the anterior thigh and the face (see Table 6).

Discussion

Meperidine, one of the phenylpiperidine derivatives of the opioids, is closer in several ways to local anesthetics than other opioids, with, for example, similar molecular weight and pKa (MW 247 and pKa 8.5 for meperidine hydrochloride, and MW 234 and pKa 7.9 for lidocaine hydrochloride) (7). Meperidine has been reported to produce peripheral nerve block (1), a reflection of its local anesthetic action. It has also been shown in many studies to have the properties of local anesthetic, both in sensory and motor blockade, after intrathecal injection (2,3). The present study shows that meperidine and lidocaine in the same dosage, volume, and concentration produced comparable effects on neural structures within the subarachnoid space. Although the onset and duration of both the sensory and motor block were significantly more rapid and longer with lidocaine, the extent of maximum spread, which indicated their distribution in cerebrospinal fluid, was similar. However, meperidine also had the other properties typical of narcotic in the form of higher frequency of both intraoperative and postoperative complications, which are attributable to its action on the central nervous system.

In the study of 20 patients reported by Famewo and Naguib (3), spinal meperidine in a dose of 1 mg/kg produced a mean maximum cephalad spread of sensory blockade to the T-7 dermatome level and was associated with complications that included decreases in arterial pressure more than 20% below the control levels (three patients), nausea and vomiting (six patients), pruritus (five patients), and difficulty in micturition (two patients). Fifteen of their patients did not require postoperative analgesic medication. In our study the level of mean maximum cephalad spread of sensory blockade, which was limited by the sitting position, was not different from that reported by Famewo and Naguib but the incidence of complications in our patients was somewhat higher. This increase may be attributable to the higher dosage of meperidine used in our study, but it is surprising that the proportion of pain-free patients did not correspond to the increase in dosage.

Intrathecal morphine at one-tenth to one-twentieth of its systemic dose generally produced a duration of analgesia between 12–24 hr in patients with either postoperative or chronic pain. The duration of analgesia produced by intrathecal meperidine, at systemic dose, was much shorter in our study because it blunted the surgical pain, which was much more intense than other types of pain. The effects of intrathecal meperidine are also made shorter by its high lipid solubility, which causes rapid efflux into venous and lymphatic clearance channels (7).

The cost of meperidine, a local product in our country, is less than half the cost of lidocaine–glucose, which is imported. Even with the addition of one ampule of metoclopramide necessitated by the high incidence of intraoperative nausea and vomiting the costs are still less than three-fourths the price of lidocaine–glucose. Meperidine as the sole intrathecal anesthetic agent for surgery may be useful because of its lower expense but this is offset by the higher incidence of complications with which it is associated.

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Note Added in Proof

After this paper was accepted for publication, a closely related paper appeared by Acalovschi et al. Spinal block with pethidine for perineal operations. Br J Anaesth 1986;58:102–6.

ANESTH ANALG
1987;66:241–4

Respiratory Effects of Sevoflurane

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DOI M, IKEDA K. Respiratory effects of sevoflurane. Anesth Analg 1987;66:241–4.

The respiratory effects of sevoflurane were studied in seven patients and compared with values obtained in another seven patients anesthetized with halothane. Resting ventilation, resting Pa_{CO_2}*, and ventilatory response to* CO_2 *were measured awake and at 1.1 and 1.4 MAC levels of both anesthetic agents. We found that with sevoflurane, tidal volume and the slopes of the* CO_2 *response curves decreased and* Pa_{CO_2} *increased with increasing depth of anesthesia, as with other inhaled anesthetics. A compensatory increase in respiratory frequency was not enough to prevent a decrease in minute volume with increasing depth of anesthesia. At 1.1 MAC, sevoflurane produced almost the same degree of respiratory depression as halothane. At 1.4 MAC, sevoflurane produced more profound respiratory depression than halothane.*

Key Words: ANESTHETICS, VOLATILE—sevoflurane. VENTILATION—sevoflurane.

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) is a potent halogenated ether recently introduced for clinical phase-2 study as a general anesthetic agent. Its low blood gas partition coefficient of 0.60 (1) provides rapid induction of anesthesia (2). The metabolism of sevoflurane (1,3–12), the relationship between sevoflurane and malignant hyperthermia (13,14), and the mutagenicity of sevoflurane (15) have been studied extensively. The respiratory effects of sevoflurane in humans, however, have not been examined, with the exception of a preliminary phase-1 study (8). In our experiments with dogs we found that sevoflurane might be a profound respiratory depressant (16). The present study was undertaken to evaluate more thoroughly the ventilatory responses to sevoflurane in patients scheduled for minor surgery and to compare these with those associated with halothane.

Methods

Fourteen patients scheduled for a minor surgery on the head or neck were studied. This study was approved by the institutional human research committee of Hamamatsu University Hospital. Seven patients were given sevoflurane and seven were given halothane anesthesia. There were no significant differences in age, height, weight, or the duration of anesthesia between the 2 groups (Table 1). The subjects fasted for at least 11 hr before anesthesia and received no premedicant drugs. A catheter was placed into a radial artery under local anesthesia. A semiclosed anesthetic circle system assembled with an F breathing circuit (17) was used. A mass spectrometry sampling tube and an electric Wright respirometer (BOC Co., Ltd.) were placed between the breathing circuit and the mask or endotracheal tube. Output from the Wright respirometer was linearized using the system developed by Sanjo et al. (18) so that reliable measurements were attained even at low flow rates. A Perkin Elmer MGA-1100 was used for a mass spectrometry. The respirometer and mass spectrometer were used to measure minute volume ($\dot{V}_E$ BTPS), respiratory frequency (f), inspired CO_2 concentration ($F_{I_{CO_2}}$), end-tidal CO_2 concentration ($F_{ET_{CO_2}}$), inspired anesthetic concentration, and end-tidal anesthetic concentration.

The Wright respirometer and a connector for the gas sampling tube created a mechanical dead space of 40 ml. Tidal volume (V_T BTPS) was calculated by dividing minute volume (BTPS) by respiratory frequency. A bypassed minimixing chamber developed by Sanjo et al. (18) was placed between the expiratory end of the breathing circuit and the expiratory valve of the anesthetic machine. Using the bypassed minimixing chamber, fluctuating expiratory CO_2 concentration was smoothed out and became flat mean expired CO_2 concentration. Mean expired CO_2 concentration ($F_{E_{CO_2}}$) was then measured through mass spectrometry. Before anesthesia was induced, pa-

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Table 1. Patient Demographics

	Sevoflurane	Halothane
Number of subjects (M/F)	7 (3/4)	7 (4/3)
Age (yr)	47.6 ± 3.3	44.7 ± 5.1
Height (cm)	158.0 ± 2.6	160.7 ± 2.5
Weight (kg)	51.3 ± 3.1	55.6 ± 4.0
Anesthesia time (min)	171 ± 35	175 ± 33

All values given as means ± SEM.

tients breathed 35–40% oxygen and 60–65% nitrogen through the anesthetic circuit by mask for 5 min, at the end of which ventilatory measurements were stable. An arterial blood sample for measurement of gas tensions was obtained. Minute CO_2 elimination ($\dot{V}CO_2$), minute alveolar ventilation ($\dot{V}A$), the ratio of dead space ventilation (VD) to tidal volume (VT), alveolar ventilation (VA), and dead space ventilation (VD) were calculated using the following equations:

$$\dot{V}CO_2 = \dot{V}E(STPD) \times FE_{CO_2} \quad (1)$$

$$\dot{V}A = \dot{V}E\ (BTPS) \times PE_{CO_2}/PaCO_2 \quad (2)$$

$$VA = \dot{V}A/f \quad (3)$$

$$VD = VT - VA \quad (4)$$

$$VD/VT = PaCO_2 - PE_{CO_2}/PaCO_2 \quad (5)$$

After these measurements, inspired CO_2 concentration was increased sufficiently to increase end-tidal CO_2 tension by 2–4 torr. After at least 6 min had elapsed at the new end-tidal CO_2 tension, minute volume and respiratory frequency were again recorded, and then another arterial blood sample was obtained. Inspired CO_2 concentration was then increased sufficiently to increase end-tidal CO_2 tension by 4–6 torr above the prior value, and the same measurements repeated. From the two points of increased end-tidal PCO_2, the slopes of ventilatory response to CO_2 were calculated as control values before the induction of anesthesia. The resting point (no increase in inspired CO_2) was not included in the calculation of the slope. Anesthesia was then induced by mask with sevoflurane in oxygen or halothane in oxygen. The trachea was intubated with 40–60 mg of succinylcholine chloride. Intraoperatively, anesthesia was maintained with sevoflurane, 35–40% oxygen and 60–65% nitrogen, or halothane, 35–40% oxygen and 60–65% nitrogen. After the effects of succinylcholine chloride had worn off, respirations were spontaneous throughout the study. To avoid possible effects of surgical stimulation on respiration (19), the resting ventilation and respiratory responses to CO_2 during anesthesia were examined after the respiratory parameters had returned to stable levels after completion of surgery.

Assuming that the end-tidal anesthetic concentration is equal to the alveolar anesthetic concentration, the first measurements were made at 1.1 MAC (end tidal concentrations of sevoflurane and halothane, 1.88 and 0.85%, respectively). After at least 15 min of stable end-tidal anesthetic levels, minute volume, respiratory frequency, and FE_{CO_2} were recorded, and an arterial blood sample was drawn. Inspired CO_2 concentration was then added to increase end-tidal CO_2 tension by 8–10 torr. After at least 6 min had elapsed at the new end-tidal CO_2 tension, minute volume and respiratory frequency were again recorded and another arterial blood sample was obtained. From these two measurements, the slopes of ventilatory responses to CO_2 were calculated. The alveolar anesthetic concentration was then increased to 1.4 MAC (end-tidal concentrations of sevoflurane and halothane, 2.39 and 1.08%, respectively), and ventilatory measurements were again made after at least 15 min had passed. There the MAC of halothane was assumed to be 0.77% (20), and the MAC of sevoflurane 1.71%, as recently determined in our department (unpublished observations).

For intragroup comparisons, the values were analyzed by Student's paired *t*-test and for intergroup comparisons the values were analyzed by Student's *t*-test. Statistical significance was assumed when $P < 0.05$.

Results

During sevoflurane anesthesia, tidal volume decreased with increasing depth of anesthesia (Table 2). Respiratory frequency increased but not enough to fully compensate for the decrease in the tidal volume. As a result, minute volume also decreased with the increase in anesthetic depth. However, during halothane anesthesia, tidal volume decreased, as with sevoflurane, with increased anesthetic depth but respiratory frequency increased to the extent that there was no significant change in minute volume. At 1.1 MAC, respiratory frequency during sevoflurane anesthesia was significantly less than with halothane anesthesia. At 1.4 MAC, respiratory frequency and minute volume during sevoflurane anesthesia were significantly less than with halothane anesthesia. Tidal volumes were similar with both anesthetics at equal anesthetic depths. On the other hand, when anesthetic depth was increased to 1.4 MAC from 1.1 MAC, the slopes of the ventilatory responses to CO_2 became flatter with both anesthetics, but at 1.4 MAC, sevoflurane produced a significantly flatter slope of the CO_2-ventilatory response curve than did halothane.

There were no significant differences in $PaCO_2$ between the anesthetics at 1.1 MAC. At 1.4 MAC, how-

Table 2. Effects of Sevoflurane and Halothane Anesthesia on Respiration

	Sevoflurane			Halothane		
	Awake	1.1 MAC	1.4 MAC	Awake	1.1 MAC	1.4 MAC
Number of subjects	7	7	7	7	7	7
F_{ET} Anes (%)	—	1.88 ± 0.02	2.39 ± 0.03	—	0.85 ± 0.01	1.09 ± 0.01
Anesthesia time (min)	—	114 ± 27	157 ± 34	—	125 ± 26	161 ± 35
Pa_{CO_2} (torr)	39.4 ± 1.4	48.8 ± 1.9[a]	54.8 ± 2.3[a,b,c]	38.7 ± 0.6	46.7 ± 0.9[a]	49.5 ± 1.4[a,b]
$\dot{V}_E$ (l/min)	5.96 ± 0.15	5.30 ± 0.30[a]	4.45 ± 0.25[a,b,c]	6.13 ± 0.25	5.34 ± 0.30[a]	5.60 ± 0.32
V_T (ml)	489 ± 30	247 ± 13[a]	189 ± 8[a,b]	483 ± 27	204 ± 15[a]	181 ± 9[a,b]
f (breaths/min)	12.4 ± 0.6	21.7 ± 1.1[a]	23.7 ± 1.3[a,b,c]	12.9 ± 0.4	26.7 ± 1.1[a]	31.0 ± 1.1[a,b]
S ($l \cdot min^{-1} \cdot torr^{-1}$)	1.73 ± 0.12	0.60 ± 0.14[a]	0.17 ± 0.04[a,b,c]	1.85 ± 0.18	0.51 ± 0.07[a]	0.31 ± 0.06[a,b]
$\dot{V}_{CO_2}$ (ml/min)	186 ± 6	151 ± 7[a]	110 ± 6[a,b]	191 ± 5	152 ± 6[a]	127 ± 4[a,b]
$\dot{V}_A$ (ml/min)	3380 ± 98	2220 ± 110[a]	1440 ± 106[a,b]	3530 ± 110	2310 ± 60[a]	1830 ± 60[a,b]
V_D/V_T (%)	43.0 ± 1.8	57.9 ± 2.2	67.4 ± 1.7[b]	39.7 ± 2.0	55.8 ± 2.3	66.7 ± 1.5[b]
V_A (ml)	279 ± 20	104 ± 8[a]	62 ± 5[a,b]	279 ± 10	89 ± 5[a]	59 ± 3[a,b]
V_D (ml)	209 ± 15	143 ± 9	127 ± 6[b]	193 ± 21	116 ± 12	121 ± 7[b]

All values given as means ± SEM. Differences considered statistically significant when $P < 0.05$.

F_{ET} Anes, End tidal anesthetic concentration. S, Slope of CO_2 response curve.

[a] Differs from awake value.

[b] Differs from 1.1 MAC value.

[c] Differs from halothane at the same anesthetic depth.

ever, Pa_{CO_2} was significantly higher with sevoflurane anesthesia than with halothane. When anesthetic depth was increased, there was a decrease in CO_2 elimination with both anesthetics. The decrease in CO_2 elimination was similar with both anesthetics at both levels of anesthesia but greater at 1.4 MAC than at 1.1 MAC.

V_D/V_T ratios before and after anesthesia could not be reliably compared because the ratio measured before anesthesia was performed through the mask with subsequent measurements being made via the endotracheal tube, therefore there were differences in the mechanical dead spaces between the two settings. However, V_D/V_T ratios increased due to decreases in tidal volumes with increasing depth of anesthesia with both anesthetics, but the changes in V_D/V_T ratios were not significantly different between sevoflurane and halothane at equal MAC levels. Similarly, no significant differences were observed in V_A and V_D with sevoflurane and halothane. Table 2 also shows that there was no significant difference in times between anesthetic induction and when measurements were made in the two groups of patients.

Discussion

A possible limitation in the present study is that measurements made during anesthesia were performed after surgery had been completed. In order to minimize surgical effects that might affect the experimental results, we limited experimental subjects to patients having only minor surgery on the head or neck (e.g., tympanoplasty). Another possible limitation is that respiratory changes associated with general anesthesia have been reported as being related to the duration of anesthesia, even in the presence of constant alveolar anesthetic concentrations (21). For this reason, we carried out each set of measurements in both groups of patients at times when the duration of anesthesia was as close as possible given the clinical conditions under which we had to conduct our study.

Finally, in this experiment we sampled end-tidal gas from the connector mounted on the slip joint of the endotracheal tube and took the value of the end-tidal anesthetic concentration as the alveolar anesthetic concentration. This method raises the possibility that dead space gas might have mixed with alveolar gas as tidal volume decreased, thereby causing the "end-tidal anesthetic concentration" to be greater than true alveolar anesthetic concentration. However, tidal volumes were similar with both anesthetics at both 1.1 MAC and 1.4 MAC levels. Because of this, it is likely that the difference between the alveolar anesthetic concentrations and the end-tidal anesthetic concentrations were similar with both anesthetics and thus did not affect the comparison of respiratory effects of sevoflurane and halothane at the same anesthetic depth.

We found that sevoflurane produces respiratory depression with increasing depth of anesthesia, as with other types of inhaled anesthetic agents. The characteristics of the respiratory effects of sevoflurane are that tidal volume decreases with increasing depth of anesthesia and that this decrease is not adequately compensated for by an increase in the respiratory frequency, at least between 1.1 MAC and 1.4 MAC. These characteristics agree with the results we obtained from experiments with dogs (16). Also, the characteristics of the ventilatory depression associated with sevoflurane are similar to the reported ventilatory effects of isoflurane (21). In comparing ventilatory responses to sevoflurane and halothane, we found no significant differences with both anesthetics at 1.1 MAC, but observed that sevoflurane caused greater respiratory depression than did halothane at 1.4 MAC. CO_2 elimination decreased with an increase in the anesthetic depth with both anesthetics. This does not imply that CO_2 production decreased. The time associated with changes in ventilatory conditions was too short to allow establishment of a steady state adequate for CO_2 homeostasis. We also found that both anesthetics have similar effects on VD/VT, VD, and VA at equal anesthetic depth. There is, therefore, no significant difference between halothane and sevoflurane in terms of effects on tidal volume.

This experiment indicates that sevoflurane is a greater respiratory depressant than halothane at 1.4 MAC. In general, sevoflurane and halothane are clinically used in combination with nitrous oxide. When sevoflurane or halothane are used with nitrous oxide, the alveolar anesthetic concentration aimed at is generally about 1 MAC. We could find no evidence in our study to suggest that sevoflurane and halothane have clear differences in the respiratory depression they cause at 1.1 MAC. Thus it is not clear whether sevoflurane is a more profound respiratory depressant than halothane in clinical use. This suggests that we should examine further interactions of sevoflurane or halothane (or both) used in combination with nitrous oxide and other drugs.

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Effect of Morphine on the Mechanical Activity of Common Bile Duct Isolated from the Guinea Pig

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VATASHSKY E, HASKEL Y, NISSAN S, HANANI M. Effect of morphine on the mechanical activity of common bile duct isolated from the guinea pig. Anesth Analg 1987;66:245–8.

The contractile response of isolated guinea pigs common bile ducts (CBD) to transmural electrical stimulation and the effects of morphine and naloxone was studied. Contractile responses increased as a function of stimulus frequency. In the absence of naloxone morphine inhibited the contractile response to electrical stimulation in a dose-dependent manner. Naloxone prevented the inhibitory effect of morphine on the contractile response to electrical stimulation. We conclude that smooth muscle of the CBD in guinea pig is functional and can contribute to biliary motility, and that opiate receptors exist in nerve elements in the CBD.

Key Words: LIVER—bile ducts. ANALGESICS—morphine.

It is well known that morphine increases intraductal pressure via a spasmogenic effect on the choledochoduodenal junction (1). However, it is not known whether this action is due to an effect on the duodenum only or on the sphincter of Oddi. The paralyzing effect of morphine on the guinea pig intestine can be explained by inhibition of the release of acetylcholine (ACh) from the intrinsic nerve of the gut (2), but the mechanism of the effect of morphine on the biliary tract is not clear.

Most studies of the physiology and pharmacology of extrahepatic biliary ducts have been done intraoperatively in humans (3,4), in vivo in animals by measuring pressure responses in the common bile duct (CBD) to systemically injected narcotics (5,6), or in vitro while perfusing the CBD and recording pressures (7.8). The results of these studies depend on the route of administration of the narcotics. Thus, when morphine-like drugs are injected intravenously as a component of intraoperative analgesia (3) or for postoperative pain relief (9), CBD pressure increases significantly, occasionally leading to development of a false roentgenologic picture of biliary tract stones or to biliary colic with subsequent needless exploration for choledocholithiasis (10). On the other hand, when narcotics are injected epidurally (6) in humans or intraarterially in cats (8) the tone of the sphincter of Oddi is unchanged. It has been suggested that the variability in response of biliary tract tissue to narcotics may be due to the presence of opiate receptors in the biliary tree itself. The occupation of these receptors by narcotics depends upon the route of administration of the narcotics.

The presence of opiate receptors in the intestine is well established (11). However, information is lacking regarding the involvement of opiate receptors in the normal functioning of the biliary tree. Intrinsic ganglion cells have been demonstrated histologically in the guinea pig's CBD (12), and Ludwick (13) has proposed that they play a role in the control of CBD motility. We, therefore, decided to employ the guinea pig as a model for studying drug actions on the CBD. In the present work we looked at the effects of morphine on nerve-mediated responses.

Methods

Twenty-one adult male guinea pigs (350–600 g) were used in this study. They were killed by a blow on the head and bled. The CBD without its terminal portion (the sphincter of Oddi) was isolated and removed from the animal. Each preparation was set vertically between two platinum ring electrodes in a 10-ml organ bath by tying its lower end to a tissue holder that could be raised or lowered by the adjustment of a screw micrometer, and by tying its upper end to an isometric force transducer (Statham, Model UC-2). The

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organ bath was filled with Krebs solution of the following composition (in mM): NaCl, 120.7; KCl, 5.9; $MgCl_2$, 1.2; $CaCl_2$, 2.5; NaH_2PO_4, 1.2; $NaHCO_3$, 15.5; glucose, 11.5. The solution was bubbled with a gas mixture of 95% O_2 and 5% CO_2; the pH was 7.4 and the temperature was 37°C ± 0.5. The preparations were electrically stimulated (Grass Stimulator, Model S-88) with pulses of 0.5 msec width. The duration of each stimulus was 15 sec. Responses were recorded on a Could Recorder, Model 2200-S.

In a pilot study the optimal conditions of electrical stimulation of isolated guinea pig CBD were studied. The threshold intensity of stimulation was found to be 10 V. The amplitude of responses increased with the stimulus intensity until a plateau was attained at 40 V. This voltage was then used in all subsequent experiments. Frequencies below 0.1 Hz did not produce consistent responses. In the experiments described below we used frequencies between 0.1–5 Hz.

Before drugs were added the preparations were allowed to equilibrate for 1 hr under a tension of 0.5 g. We also found that concentrations of morphine hydrochloride below 0.1×10^{-6} g/ml had no measurable effect on the response of CBD to electrical stimulation; therefore, in the present study morphine was added to the bath in concentrations ranging between 0.1×10^{-6} and 2×10^{-6} g/ml. Naloxone was added in concentration range between 0.01×10^{-6} and 0.1×10^{-6} g/ml. Each drug was left in contact with the tissue for 1 min before the electrical stimuli were applied. The preparation was washed three times during the following 30 min, and new control values were recorded before the next drug application.

The experiment was designed as follows: 1) control responses of CBD to electrical stimulation at various frequencies (in the range between 0.1 and 5 Hz) were measured; 2) the effects of various concentrations of morphine on the responses of the CBD were measured; and 3) the effect of naloxone on the inhibitory action of morphine on the response of the CBD to electrical stimulation was recorded. To produce the reversal effect of naloxone on the morphine-induced inhibition the preparations were stimulated at constant frequency of 1 Hz, morphine was added at concentration of 1×10^{-6} g/ml, and naloxone in increasing concentrations was added after the inhibitory effect of morphine was recorded.

Because responses to morphine are not completely reversible in vitro (11) the responses during each run at a given concentration of morphine or naloxone were compared with that of a baseline value established immediately before the concentrations changed, i.e., after three washings. Responses were measured as a function of stimulus frequency before and during exposure to morphine. The effect of morphine is expressed as the ratio (in percent) of the amplitude during and before morphine administration for each frequency. The drugs used were morphine hydrochloride (Teva Pharmaceutical Industries, Israel) and naloxone (Du Pont De Nemours), and the figures represent their final concentrations in the bath. The results from up to 15 experiments were used for calculating the effects (mean ± SE) of morphine at various frequencies.

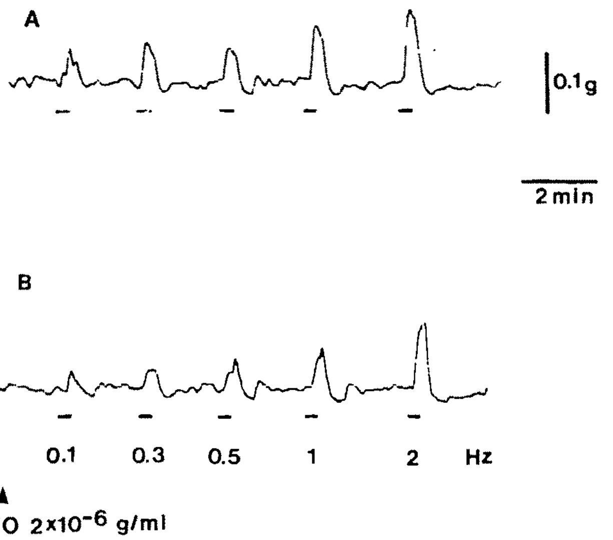

Figure 1. Contractile responses of the guinea pig's isolated common bile duct to electrical stimulation. Contractile responses were recorded by isometric force-transducer. The stimulus duration is indicated by the horizontal bars.
(A) Control responses at various stimulus frequencies.
(B) Morphine (2×10^{-6} g/ml) inhibited responses to electrical stimulation.

Results

Figure 1*A* shows a sample of responses of the isolated CBD to electrical stimulation. The responses clearly increased as the frequency was increased from 0.1 to 5 Hz (Table 1). Repeated stimulations at all frequencies for 1–2 hr produced stable responses in untreated tissues.

When morphine was added to the bath the responses of the CBD preparations to electrical stimulation were decreased below those observed before morphine was added (Fig. 1*B*). Significant inhibition was observed when morphine was applied at concentrations over 0.1×10^{-6} g/ml. In spite of variations in the responses it is evident that the effect of morphine is dose-dependent (Fig. 2). This inhibition was

Table 1. Responses of Isolated Guinea Pig's Common Bile Duct to Electrical Stimulation

	Frequency (Hz)					
	0.1	0.3	0.5	1	2	5
Responses (mg)	60 ± 1.5	102 ± 3.1	112 ± 3.3	173 ± 4.5	168 ± 8.8	190 ± 6.7

Values are mean ± SE.

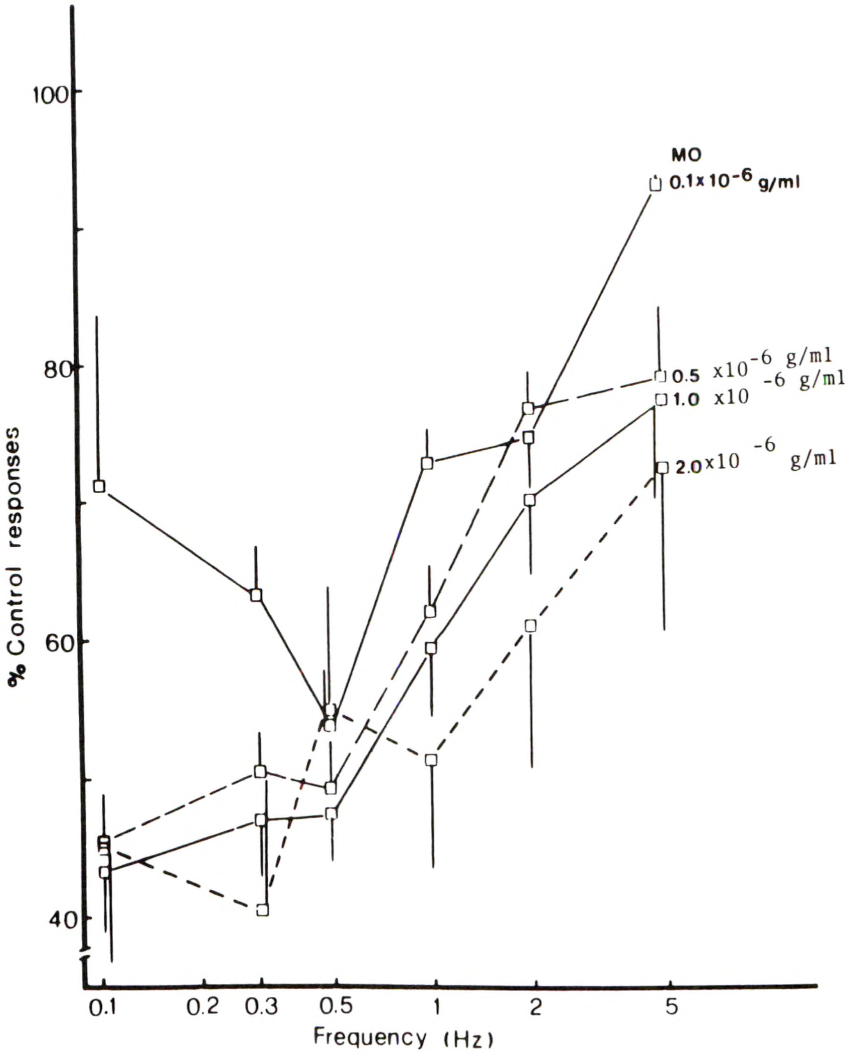

Figure 2. Effect of morphine on the responses to electrical stimulation at various frequencies (mean ± SE). Morphine concentrations were 0.1, 0.3, 0.5, 1, and 2 × 10^{-6} g/ml. Responses were measured as function of stimulus frequency before and during morphine application. The effect of morphine is expressed as the ratio (in percent) of the amplitude during and before morphine administration for each frequency. Each point is the mean of results from 6 to 15 different preparations at frequencies between 0.1 to 2 Hz, and from 4 to 5 preparations at 5 Hz.

prominent at low frequencies (0.1–1 Hz) and appears to be less at higher frequencies (Fig. 2).

In the experiment shown in Figure 3 morphine (1 × 10^{-6} g/ml) inhibited the responses to electrical stimulation at 1 Hz. Naloxone added during this inhibition caused recovery of response in a dose-dependent manner. The threshold for the naloxone effect was 0.01 × 10^{-6} g/ml and it reached saturation at the concentration of 0.1 × 10^{-6} g/ml. In a different series of experiments naloxone was applied in the same concentration range before morphine administration and it also antagonized the action of morphine.

Discussion

Most of the reports on the physiology of extrahepatic bile tracts deal with the motility of the gallbladder and the sphincter of Oddi; very few have examined the

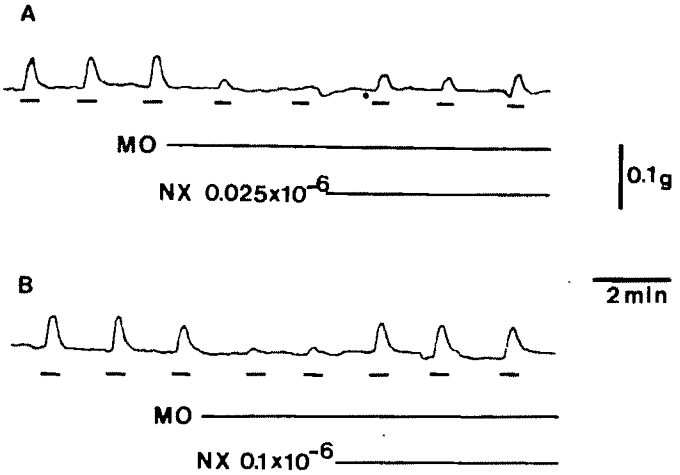

Figure 3. Naloxone reverses in a dose-dependent manner the inhibiting effect of morphine (1×10^{-6} g/ml) on the CBD's response to electrical stimulation at the frequency of 1 Hz. At a concentration of 0.1×10^{-6} g/ml it completely reversed the effect of morphine.

role of the CBD in biliary dynamics. The aim of the present study was to record the contractile responses of the longitudinal muscle in the guinea pig's CBD to transmural electrical stimulation and to measure the changes induced by morphine. The results show that the contractile responses of the CBD to transmural electrical stimulation increase with stimulus frequency, as has been seen in the isolated gallbladder (14). Also, morphine inhibited the contractile response in a concentration range of 0.1 to 2×10^{-6} g/ml. This inhibition was prevented by naloxone. The action of morphine was more prominent at low stimulus frequencies, as has been observed in the gut (2,11).

Whether the common bile duct serves as a passive conduit or whether it can, by its own intrinsic activity, contribute to the propulsion of the bile through the lumen is still the object of debate (15). There is histologic (12) and physiologic (15,16) evidence that longitudinal smooth muscle is present in CBD and contributes to its mechanical activity. The results presented in this study also suggest that muscle fibers in the wall of the common bile duct may actively modify bile flow. The inhibitory effect of morphine on the response to electrical stimulation and the inhibitory effect of naloxone on the response to morphine indicate the presence of opiate receptors in the guinea pig CBD. Similar results have been previously found in various parts of the gastrointestinal tract, and thus the present work suggests that the innervation of the CBD may be similar to that of the gut.

To the best of our knowledge this is the first demonstration of opiate receptors in the CBD in any species. It can be concluded that the guinea pig CBD is suitable as a model for studying peripheral opiate receptors, and as a tool for investigating bile dynamics. This will further clarify the mechanism of narcotics action on the extrahepatic biliary tract.

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Review Article

Perioperative Evaluation of Regional Wall Motion by Transesophageal Two-Dimensional Echocardiography

Fiona M. Clements, MD, and Norbert P. de Bruijn, MD

With the introduction of transesophageal two-dimensional echocardiography into the operating room the subject of regional left ventricular (LV) wall motion presents itself to the clinical anesthesiologist. Overwhelming evidence of the sensitivity of regional wall motion as a marker of regional myocardial perfusion suggests that it will find a place for the monitoring of patients at risk for ischemia. In this review, we define regional wall motion, normal and abnormal, and examine its relationship to regional myocardial perfusion. The practical aspects of recognizing, describing, and treating regional wall motion abnormalities will be addressed, with emphasis on transesophageal two-dimensional echocardiographic techniques.

The development of transesophageal imaging techniques has taken place only during the past 10 yr. Frazin and co-workers in 1976 reported the use of an M-mode esophageal transducer for patients in whom conventional imaging techniques failed (1). Generally, transthoracic images are technically poor when excessive adipose or lung tissue lies between the external transducer and the heart. Thus, the esophagus provided better access to the heart. Matsumoto and co-workers employed esophageal transducers in subjects performing supine bicycle exercise and also in anesthetized patients (2,3). The incorporation of the transducer into a flexible gastroscope from which the fiber optics had been removed permitted the operator to direct the ultrasound beam in multiple planes from any position within the esophagus. With the development of miniature phased array transducers, excellent two-dimensional imaging became feasible from the esophagus. Schlüter and co-workers reported their use of such a transducer in 1982 (4), and it is this type of esophageal transducer that has been used by most investigators and that has produced the images presented in this review.

Normal Wall Motion

Until recently, it was thought that the normal pattern of LV contraction was characterized by a uniform, almost concentric, inward motion of all points along the ventricular endocardium during systole (5). However, this simplistic notion has been rejected by several investigators upon examining canine and human hearts with various methods, e.g., echocardiography, cineangiography, and sonomicrometry. By echocardiography, the normal ventricular wall is seen to thicken during systole and the endocardial surface moves inward. In comparing end-diastolic and end-systolic short axis views of the left ventricle, therefore, the ventricular cavity area is seen to decrease markedly during systole as the stroke volume is expelled, and the circumference of the endocardial border is likewise decreased in the systolic view (Fig. 1).

With a real-time video display that provides 30 frames per second, the observer integrates the visual information to yield an impression of good or poor contraction. The observer learns to discount the fact that the heart may shift its position in the chest with systole, or during the course of the respiratory cycle, concentrating on the wall thickening, LV cavity shape and size. The myocardium may not be imaged well in parts of the sector arc. If the endocardial and epicardial borders are not seen (echo dropout), then the impression of no contraction may be erroneously formed. Such echo dropout is prone to occur in the lateral fields of the image where ultrasound is reflected off the myocardial walls in a haphazard fashion, producing poor cardiac definition. Similar arti-

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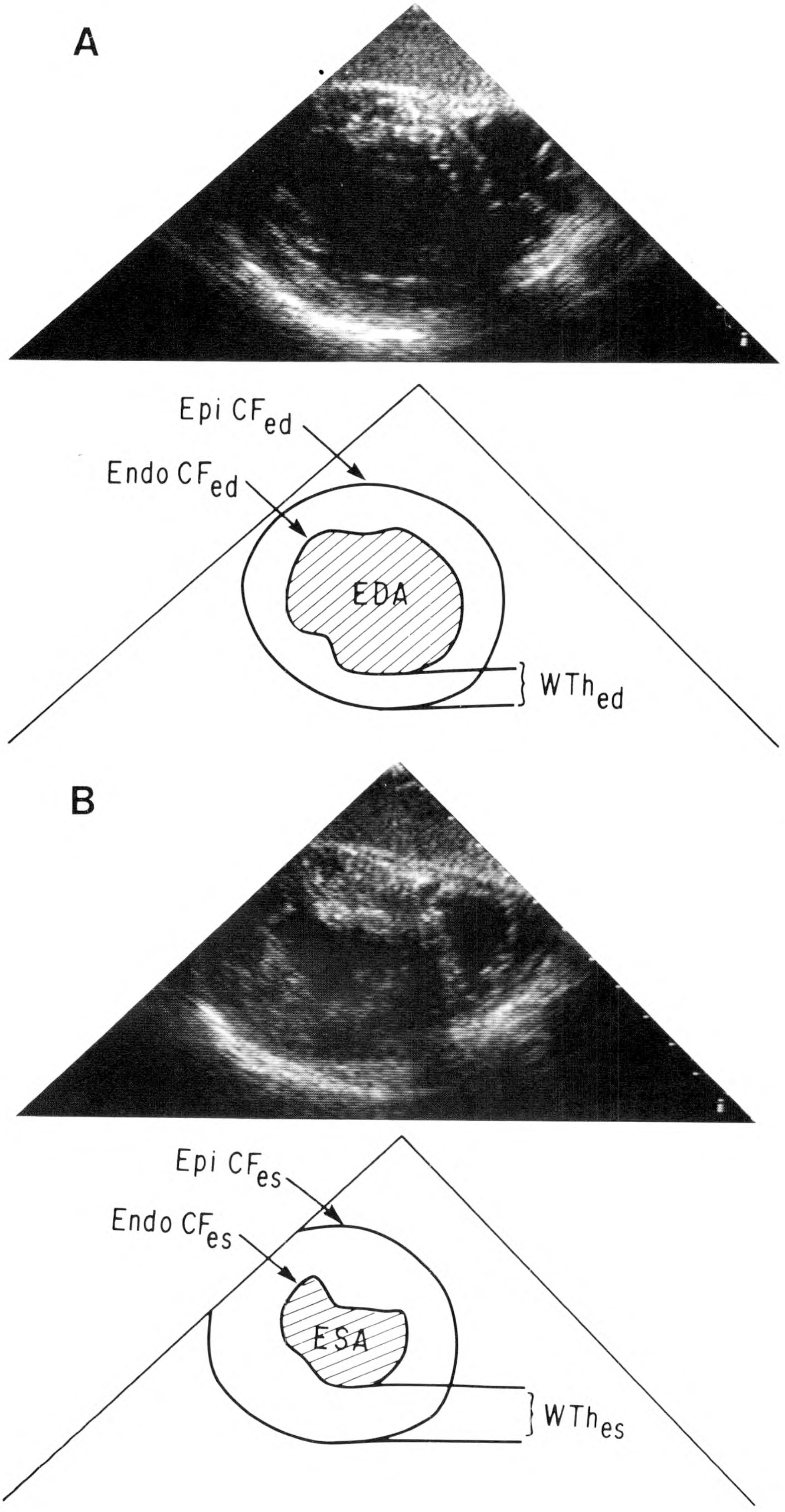

Figure 1. Left ventricular short axis image (papillary muscle level) A. Diastole. B. Systole. endo = endocardium; epi = epicardium; WTh = wall thickness; EDA = end-diastolic area; ESA = end-systolic area; CF_{ed} = end-diastolic endocardial circumference; CF_{es} = end-systolic endocardial circumference.

facts resulting from improper use of the gain controls (see later) or errors in imaging technique may lead to false interpretation of images.

Left ventricular wall motion is not entirely uniform around the ventricle. In fact, contraction increases from base to apex, as described by wall thickening, fractional area change, and circumferential shortening of the endocardium (see Table 1). These parameters may also be applied to express regional myocardial function. Haendchen et al. (6) found the fractional area change of the LV cavity to be 40% at the base of the heart, increasing to 60% at the apex. Since the diastolic area at the apex is considerably less than that of the base, it is still the base of the heart that contributes the most to stroke volume, however. Furthermore, Rankin et al. (7) have shown in the canine heart that 87% of the stroke volume is derived from shortening in the short axis of the ventricle; very little contribution to cardiac output results from shortening of the long axis. Therefore, with two-dimensional echocardiography, myocardial contraction is best studied with multiple short axis views recorded at different levels along the long axis of the left ventricle (Fig. 2).

The ventricular septum must be given separate consideration. Although normal septal wall thickening is approximately 30%, it must be realized that this refers to the muscular lower portion of the septum. There is a basal membranous part that does not exhibit the same degree of contraction. Unlike the LV free wall, the septum is also a part of the right ventricle and subject to forces from both sides. It is attached superiorly to the aortic outflow tract. When the septum is examined with multiple short axis views, it is normally found to move paradoxically in the basal portion; i.e., whereas the LV free wall moves inward during systole, the septum moves outward. Only in lower short axis views (midpapillary, low LV, apical) does it appear to move inward concentrically with the free wall. A similar paradoxical motion can also be seen during abnormal activation patterns of the ventricle, such as occurs with left bundle branch block or with ventricular pacing.

Abnormal Wall Motion

Abnormal wall motion is described by the terms hypokinesia, akinesia, and dyskinesia. Hypokinesia refers to contraction that is less vigorous than normal and generally slower. Wall thickening is diminished, as is fractional area change. Severe degrees of hypokinesia are easily distinguishable but mild hypokinesia may be quite subtle. The recognition of varying degrees of hypokinesia is often difficult in the absence of quantitative measurements. Akinesia refers to the absence of wall motion, i.e., no wall thickening and no inward endocardial motion during systole. Akinesia is easily recognizable and characterizes severe dysfunction, usually as a result of infarction. Dyskinesia describes paradoxical motion, i.e., the outward motion of a portion of myocardium during systole when it should be moving inward. Dyskinesia is the hallmark of myocardial infarction and ventricular aneurysm. The anesthesiologist monitoring for ischemia is concerned with any deterioration in the contraction pattern from normal to hypokinesia, akinesia, or dyskinesia since this suggests a corresponding deterioration in myocardial blood flow.

Table 1. Measured Parameters of Regional Wall Motion or Global Function

$$\%\ \mathrm{WTh} = \frac{\mathrm{WTh}_{es} - \mathrm{WTh}_{ed}}{\mathrm{WTh}_{es}} \times 100$$

$$\%\ \mathrm{CS} = \frac{\mathrm{Endo\ CF}_{ed} - \mathrm{Endo\ CF}_{es}}{\mathrm{Endo\ CF}_{ed}} \times 100$$

$$\mathrm{FAC} = \frac{\mathrm{EDA} - \mathrm{ESA}}{\mathrm{EDA}}$$

Abbreviations: WTh, wall thickening; WTh_{es}, end-systolic wall thickness; WTh_{ed}, end-diastolic wall thickness; CS, circumferential shortening; Endo CF_{ed}, end-diastolic endocardial circumferential length; Endo CF_{es}, end-systolic endocardial circumferential length; FAC, fractional area change, EDA, end-diastolic area; ESA, end-systolic area.

Relationship of Regional Wall Motion to Myocardial Perfusion

The classic 1935 article by Tennant and Wiggers (8) described in detail how ligation of a coronary artery resulted in an almost immediate failure of contraction in the affected myocardium. In an open-chest animal, the myocardium was seen first to develop a weak contraction, progressing to no contraction and finally to an outward bulging during systole. They described, therefore, a progression of wall motion abnormalities occurring with coronary occlusion from hypokinesia to akinesia, and finally to dyskinesia.

These immediate effects occur with tissue hypoxia and develop concomitantly with the rise in myocardial lactate that is detected in the venous drainage of an ischemic region (9). Without oxygen, the production of ATP fails and regional acidosis develops. Calcium delivery to the contractile elements is impaired and myocardial contraction becomes weakened. The onset of visible wall motion abnormalities occurs within 10–15 sec of coronary occlusion. This has been demonstrated experimentally by several investigators (10–13). In human subjects undergoing

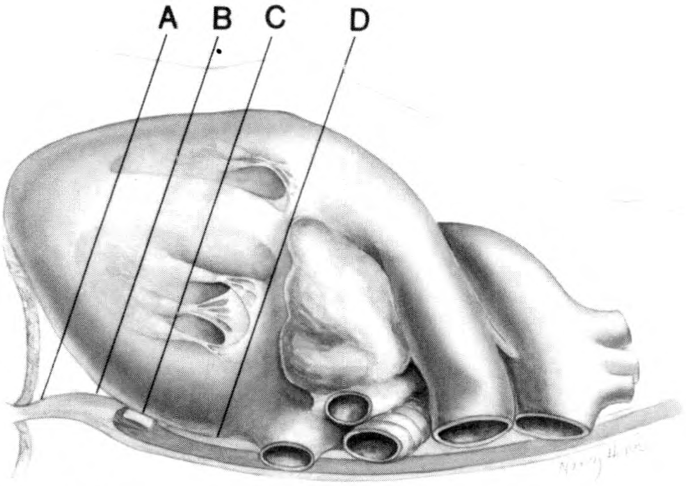

Figure 2. Transesophageal transducer in situ to record a short axis image, as illustrated in Figure 1. The alignment of the esophagus approximately parallel with the long axis of the heart allows short axis images to be recorded at several levels as indicated.

coronary angioplasty, similar findings have been reported (14). Within 15 sec of balloon occlusion of the coronary artery, hypokinesia develops. The physiologic changes responsible for contraction abnormalities are not accompanied by histologic changes until 15–20 mins of ischemia elapse. After this time, irreversible cellular changes take place that involve most cells of the area after 60 mins (15). Wall motion abnormalities observed by the anesthesiologist therefore may be reversible, when associated with a short period of ischemia, or irreversible, when associated with infarction. The progression of contraction abnormalities following coronary occlusion takes 30–60 secs to reach dyskinesia. In the instance of coronary constriction and impaired myocardial perfusion, the severity of wall motion abnormality again corresponds to the degree of perfusion abnormality. At 50% reduction of coronary flow hypokinesia develops; dyskinesia takes place with 90–95% reduction in flow. This relationship is modified by changes in heart rate, since the key to development of contraction abnormalities is really an imbalance in myocardial oxygen supply and demand: as demand increases at faster heart rates, so does the contraction abnormality appear earlier for a given degree of coronary constriction.

Sensitivity of Wall Motion Abnormalities

The surface ECG has been reported to show ST-segment elevation 30–60 secs after coronary occlusion. Therefore, if an appropriate lead is monitored, it should be possible to identify myocardial infarction almost as quickly by ECG as by two-dimensional echocardiography. Of more interest, however, is the occurrence of severe coronary ischemia, which is likely to be seen much more frequently in clinical practice. Waters and co-workers (16) found that although hypokinesia appeared first at approximately 50% reduction in coronary blood flow, ECG changes did not occur until coronary blood flow was reduced by 75%. Similar results have been reported by others (Fig. 3). In humans undergoing percutaneous transluminal coronary angioplasty, however, Alam et al. (14) reported echocardiographically diagnosed LV wall motion abnormalities in 18 out of 20 balloon occlusions. All patients who had echocardiographic changes during balloon occlusion also had concomitant ECG ST-segment elevations. The two patients without wall motion abnormalities did not have any ECG changes. Both of these patients had extensive collateral blood supply to the segment of myocardium supplied by the stenotic coronary artery.

Comparison of contractile function and ECG changes in the epicardium and endocardium further reveals that contraction abnormalities appear first in the endocardium, preceding ST-segment changes from endocardial leads (17). That ischemic manifestations should appear initially in the endocardium is not surprising. The subendocardium is known to be at greatest risk with coronary artery stenosis.

Smith and co-workers (18) compared surface electrocardiography and transesophageal two-dimensional echocardiography for detection of myocardial

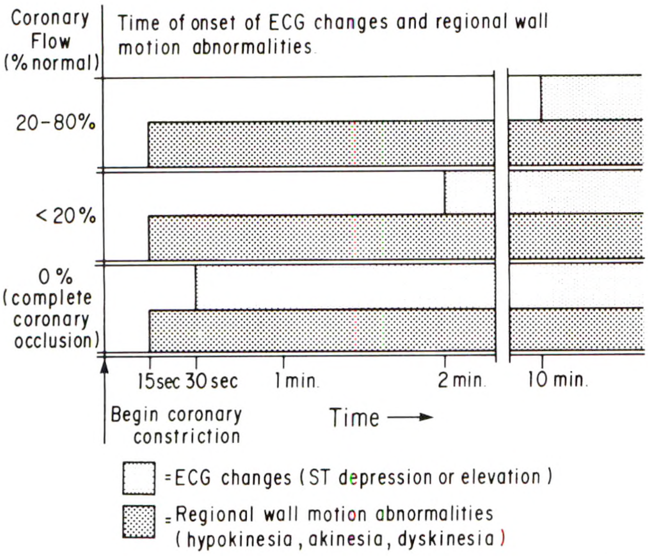

Figure 3. Temporal relationship between acute coronary constriction and onset of ECG and regional wall motion abnormalities. This figure summarizes the data from several animal and human studies (9–17).

ischemia in 50 anesthetized patients known to have coronary artery disease. Twenty-four of the 50 patients developed new segmental wall motion abnormalities intraoperatively; only six, however, developed ST-segment changes. ST-segment changes were always accompanied by wall motion abnormalities, which developed before or simultaneously with the ST-segment changes. Of the three patients who developed perioperative myocardial infarctions, only one had intraoperative ST-segment changes whereas all had persistent new wall motion abnormalities. Thus, most studies show that the sensitivity of regional wall motion abnormalities for the detection of myocardial ischemia is generally superior to that of the electrocardiogram.

Overestimation of Ischemic Area

It has been well established that acute coronary arterial occlusion results in systolic dysfunction of the myocardium in the center of the ischemic zone. However, systolic dysfunction of myocardium located at the lateral boundary of the ischemic area and in adjacent normally perfused tissue has also been reported (19). Several studies have now suggested that the total area of dysfunctional myocardium exceeds the area of infarcted myocardium. Lima et al. (20) investigated the topographic relationship between regional myocardial perfusion and function in 18 open-chest anesthetized dogs. They found that during transmural ischemia systolic wall thickening was markedly impaired in nonischemic myocardium immediately adjacent to the ischemic region and was impaired to a lesser degree in regions further away.

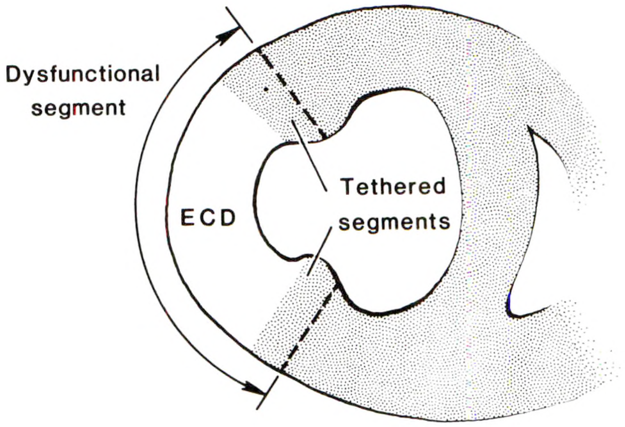

Figure 4. Diagram of short axis view of the left ventricle. Contrast medium injected into the coronary arteries enhances myocardium (shaded area). ECD = echo contrast defect, identifying nonperfused ischemic myocardium. Note that the dysfunction extends beyond the true ischemic area indicated by the ECD. Tethering accounts for dysfunction occurring in normally perfused myocardium situated adjacent to the ischemic zone.

The impairment of function in nonischemic tissue has been thought to be caused by a tethering effect, meaning that the attachment of noncontracting, infarcted tissue mechanically impairs contraction in normally perfused adjacent tissue. Wyatt et al. (21) suggested that ischemic muscle fibers parallel to nonischemic fibers might function as a parallel resistance, resulting in impaired shortening of adjacent normal fibers. Studies using sonomicrometry, on the other hand, have suggested that tethering is a relatively unimportant phenomenon (22). Recently, Force et al. (23) used contrast echocardiography to delineate in vivo the border between ischemic and nonischemic myocardium. Injection of contrast material into the coronary circulation results in enhancement of the echo density of the normally perfused myocardium on the echocardiographic image. In this study, tethering was defined as systolic dysfunction of border myocardium that enhanced with contrast. It was found in 12 dogs that the echo contrast defect (ECD), delineating the ischemic region, occupied 32% of the myocardial circumference. Tethering accounted for 4% of the circumference, involving less than 1 cm on either side of the ECD (Fig. 4). The authors concluded that tethering leads to an unavoidable overestimation of infarct size but involves a small and relatively predictable amount of myocardium.

Studies comparing the areas of contractile dysfunction with pathologic evidence of myocardial perfusion abnormalities have relied on postmortem evidence of infarction. Matching of contraction abnormalities that occur antemortem requires the use of internal landmarks on the images, which may be distorted by postmortem processing, thus making the comparisons less valid. Further, it is well known that after a period of impaired myocardial perfusion sufficient to cause ischemia but not infarction, contraction abnormalities may persist for a long time (24,25,27). Coronary occlusions of 15 min have resulted in hypokinesia persisting for 6 hr or longer (stunned myocardium) (27). Such reperfusion abnormalities can lead to overestimation of infarct size in the experimental model, and also in clinical situations now frequently encountered.

At least some overestimation of ischemic area may be caused by limitations inherent in analysis procedures used to evaluate regional LV function from two-dimensional echocardiographic images. Force and co-workers (23) found that the standard analysis algorithms exaggerated the tethering effect, in their study increasing the size of the dysfunctional segment from 32% to 39% of the myocardial circumference.

Regional Wall Motion to Guide Therapy

Having discovered the sensitivity of regional wall motion to myocardial perfusion, anesthesiologists are now interested in using echocardiography to guide therapy. There are a number of studies in the literature that examine the effects of drugs on wall motion of the ischemic myocardium. Morrison et al. (28) reported the use of M-mode echocardiography in patients with coronary artery disease to determine the reversibility of posterior wall asynergy after administration of sublingual nitroglycerin. Komer and colleagues (29) also studied the effects of nitroglycerin on regional LV performance in open-chest dogs during acute myocardial ischemia. Transient occlusion of the left anterior descending coronary artery caused end-diastolic thinning and a marked reduction in systolic thickening in the central ischemic zone. In their study, nitroglycerin did not improve regional myocardial performance in this model of the acutely ischemic canine myocardium. Kerber and co-workers (30) examined LV wall stress and found that it was nearly doubled in the ischemic region after coronary occlusion but was lowered to control levels by both nitroglycerin and nitroprusside. These effects should be beneficial because the decrease in wall stress and the resultant reduction of myocardial oxygen consumption is an important mechanism for the reduction of myocardial injury after coronary occlusion. In another study, Kerber et al. (30) reported that positive inotropic agents have two opposing effects on the dyskinesis of acutely ischemic myocardium—increased aneurysmal bulging during isometric contraction but improved wall velocity during ejection. Echocardiography has been used to evaluate the effect of inhalation anesthetics on global LV function (32,33), but not specifically on regional wall motion. These various studies indicate that two-dimensional echocardiography may be advantageous for the immediate assessment of pharmacologic interventions. Similarly, the effects of surgical interventions may be assessed. The effects on cardiac function of cross-clamping the abdominal aorta have been studied (34), and the immediate effects of coronary artery bypass grafting or valve replacement may be evaluated in the operating room.

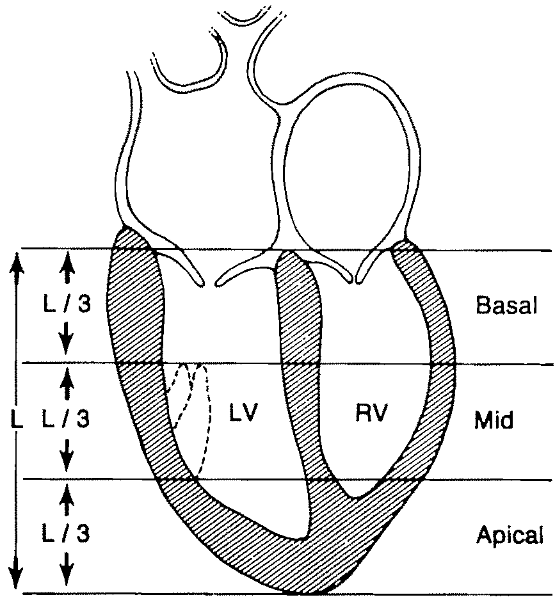

Figure 5. Division of the long axis view of the heart into three parts, as recommended by the American Society of Echocardiography (diagram adapted to transesophageal orientation). L/3 = one-third of cardiac long axis length.

Qualitative Assessment of Regional Wall Motion

Clinical, qualitative real-time examination of two-dimensional images for segmental wall motion abnormalities requires systematic, segment-by-segment examination for systolic wall thickening and endocardial motion. The identification of specific cardiac segments has been hampered by the lack of standard nomenclature for transesophageal views. Most investigators have adapted the recommendations of the American Society of Echocardiography (35) in which the left ventricle is divided into three parts along its long axis (Fig. 5). These are termed the basal, mid, and apical

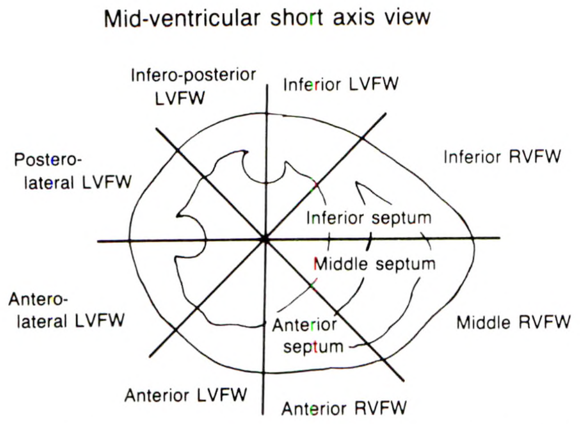

Figure 6. Division of the short axis view of the heart into eight segments as recommended by the American Society of Echocardiography, LVFW = left ventricular free wall; RVFW = right ventricular free wall.

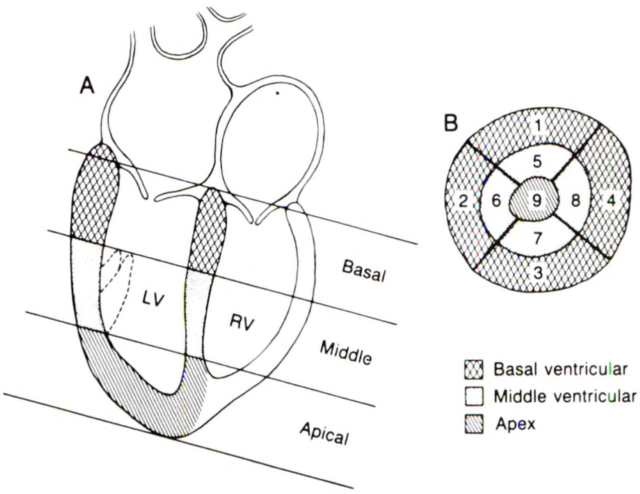

Figure 7. Simplified segmental division of the left ventricle into nine segments. [Adapted from Heger et al, (26).]

regions; the basal portion extends from the mitral valve annulus to the tips of the papillary muscles, the midportion extends from the tips to the bases of the papillary muscles, and the apical region constitutes the remainder of the ventricle. Cross-sectional or short axis views of the left ventricle can be obtained at multiple levels from the mitral valve annulus to the apex. With transesophageal echocardiography, this is accomplished by advancing the transducer along the esophagus. The LV image appears circular in cross section, with the interventricular septum accounting for 40% of its circumference. Although the septum constitutes a part of both ventricles, its thickness and spatial configuration suggest that it is an anatomic and functional part of the left ventricle. The American Society of Echocardiography has recommended division of the myocardial wall into eight segments on the short axis image, except for the apical image, which is divided into four segments (Fig. 6). Thus, 20 LV segments are defined when the three short axis levels are considered. For simplicity, the LV wall can be divided on the basal and midventricular short axis images into four segments only—anterior, lateral, inferior, and septal.

Heger and Weyman (36) correlated regional wall asynergy with the site of myocardial infarction in 37 patients; they considered the left ventricle in nine segments, dividing basal and midpapillary muscle short axis images into four segments each and leaving the apex as one segment (Fig. 7). The most frequently involved segments were those in the midpapillary muscle short axis image, followed by the apical segment. The midpapillary short axis view, therefore, which includes segments of myocardium representing all three coronary arteries, appears to be the best single view with which to monitor regional wall motion abnormalities associated with ischemia. Nevertheless, it should be realized that monitoring only one view necessarily results in a failure to detect wall motion abnormalities that may develop at other levels of the ventricle. If the patient's coronary anatomy is known from coronary angiography, an appropriate level for monitoring segments at risk may be selected. The appearance of significant wall motion abnormalities is usually obvious, but subtle changes may be difficult to pinpoint unless images can be compared over time. Some echocardiographs allow up to four images to be recalled to the video screen for this purpose.

Although anesthesiologists unfamiliar with two-dimensional echocardiography may question their ability to recognize wall motion abnormalities on the video image, we have found that this skill is easily acquired. We exposed a group of 53 clinicians (anesthesiologists, residents, and CRNAs) to 20 min of instruction about transesophageal echocardiography and the recognition of regional wall motion abnormalities. With this background, they were asked to grade regional wall motion for 12 videotape recordings and their scores were compared with those of four trained observers. The 53 clinicians correctly identified 95% of the regional wall motion abnormalities. They correctly assessed 62% of the normally contracting regions; the incorrect responses (38%) most frequently were hypokinesia (32%), the mildest grade of abnormality (37).

Quantitative Assessment of Regional Wall Motion

Two-dimensional echocardiography is very suitable for the assessment of regional wall motion because the entire left ventricle can be seen by a combination

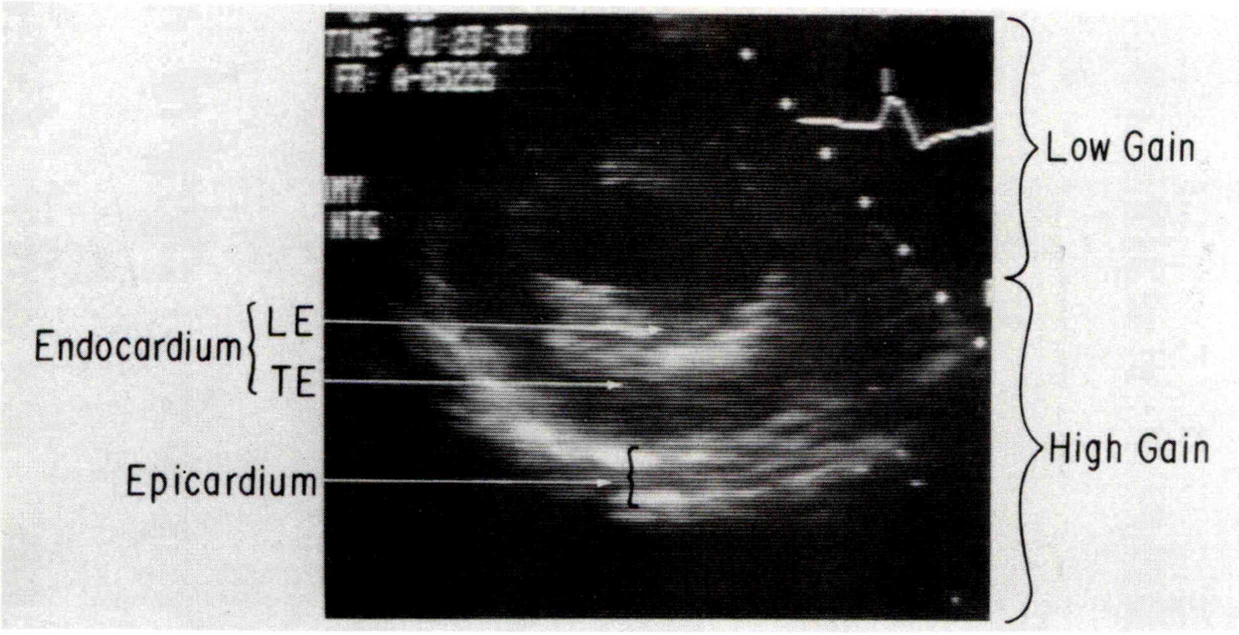

Figure 8. Short axis image to show leading and trailing edges of the myocardial borders. Low gain conceals the posterior part of the LV endocardial border in the upper part of the image. High gain in the lower part of the image blurs and widens the anterior endocardial and epicardial borders. LE = leading edge; TE = trailing edge.

of views, and specifically it allows visualization of both endocardium and epicardium. Cineangiography, on the other hand, reveals only endocardial motion. Systolic wall motion abnormalities are quantified echocardiographically by endocardial motion, abnormal circumferential shortening, and systolic wall thickening (Table 1). Endocardial movement, representing LV ejection at a global level, can be used to express a regional or segmental ejection fraction.

The first step in the quantitative analysis of regional wall motion is the selection of appropriate beats. Only a sinus beat, preceded by a sinus beat, should be used for quantitative analysis in order to circumvent the problem of postextrasystolic potentiation.

The second step in the process is to define end-diastole and end-systole. End-diastole is commonly defined by gating the echocardiogram to the ECG, the frame coinciding with the peak of the R wave being used as the end-diastolic frame. End-systole is commonly defined as the frame with the smallest LV cavity area, or may be identified by gating to the peak of the T wave. Obviously, only images with at least 80–90% of the endocardium and epicardium clearly visualized can be used. These outlines are then traced on paper with a wax pen or drawn with a digitizing pad or a light pen and the resulting analog data are computer digitized for analysis. Wyatt and co-workers (38) tested several methods in vitro for the accuracy of linear and cross-sectional measurements and in vivo for LV volume reconstruction. They recorded images with high and low "gain" settings (more or less black and white in the image) and they traced the myocardial borders using several methods.

Myocardial borders imaged by echocardiography have a thickness defined by the echoes reflected by the myocardial surfaces. This thickness is magnified with high gain settings blurring the borders such that accurate tracing may become more difficult (Fig. 8). The leading edge of the border is the edge nearest to the transducer whereas the trailing edge is the one that is furthest away. Borders lying perpendicular to the ultrasound beam are well defined but those in the lateral field tend to be less well defined. Wyatt (38) compared the accuracy of tracing borders by the leading–trailing, the trailing–leading, and the leading–leading methods. The first of these methods requires the observer to trace from the leading edge of the border closest to the transducer to the trailing edge of the more distant border, traversing the middle of the echoes on the lateral field. This method, therefore, includes most of the width of the entire circumferential border. The trailing–leading method is the reverse of this, excluding almost the entire width of the border and resulting in a smaller circumferential measurement. The leading–leading method includes the width of the border nearest the transducer but excludes the border furthest away (Fig. 9).

Regression analysis of the in vitro study comparing

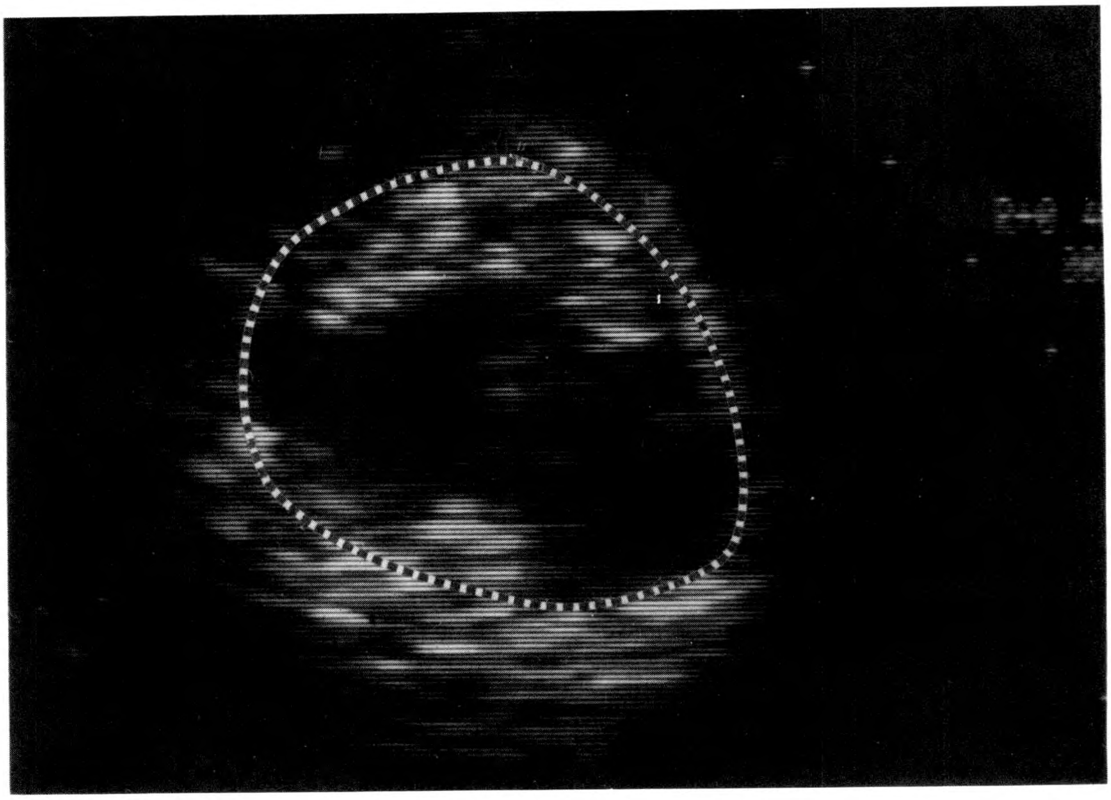

Figure 9. Short axis image of the left ventricle. The endocardial outline has been traced using the leading–leading edge method, such that the thickness of the LV posterior endocardium is included within the traced border and the thickness of the anterior endocardium is excluded. The thickness of the septum and the lateral wall are bisected by the traced line.

two-dimensional echocardiography with direct measurements yielded excellent correlations for all three methods ($r > 0.985$) with interobserver variability of $<3\%$. Accuracy of the measurements, however, was satisfactory only for the leading–leading method, which had 3% and 6% error at low and high gains, respectively. The other methods overestimated or underestimated wall thickness substantially.

It can be seen that a number of technical problems affect measurements of regional wall motion, which accounts for some of the discrepancies reported in the literature. In addition, an enormous number of computer analyses have been applied to two-dimensional images. Since the analysis of systolic wall motion requires a comparison of diastolic and systolic images, the initial step necessitates that the image borders be referenced to a specific geographic location. Fixed reference systems relate the myocardial borders to some fixed point on the video screen. This point may lie external to the cardiac image (fixed external reference) or may lie within the myocardial borders (internal reference). A fixed internal reference point in common usage is the center of mass calculated from the systolic endocardial border. If during systole the heart rotates or shifts within the chest cavity, the fixed reference systems will interpret this rotation and translation as wall motion representing myocardial contraction. Floating axis reference systems, on the other hand, attempt to correct for rotation or translation by superimposing one or two reference points identified on both the systolic and diastolic images (Fig. 10). For example, the center-of-mass analysis superimposes the diastolic and systolic centers of mass. Even this modification, however, can lead to misleading interpretations, thus tending to minimize the degree of abnormal motion.

The use of systolic wall thickening rather than endocardial movement does not completely eliminate errors. For example, Force (23) and Armstrong (26) and their associates have shown how the center-of-mass analysis can overestimate the extent of infarction by two mechanisms, namely, lengthening of an ischemic segment in systole or hypercontractility of normal tissue (excessive shortening of nonischemic segments) during systole. These common occurrences cause the ischemic segment to occupy significantly more of the LV circumference during systole than it does in diastole. With this center-of-mass analysis, the length of a dysfunctional segment is expressed as

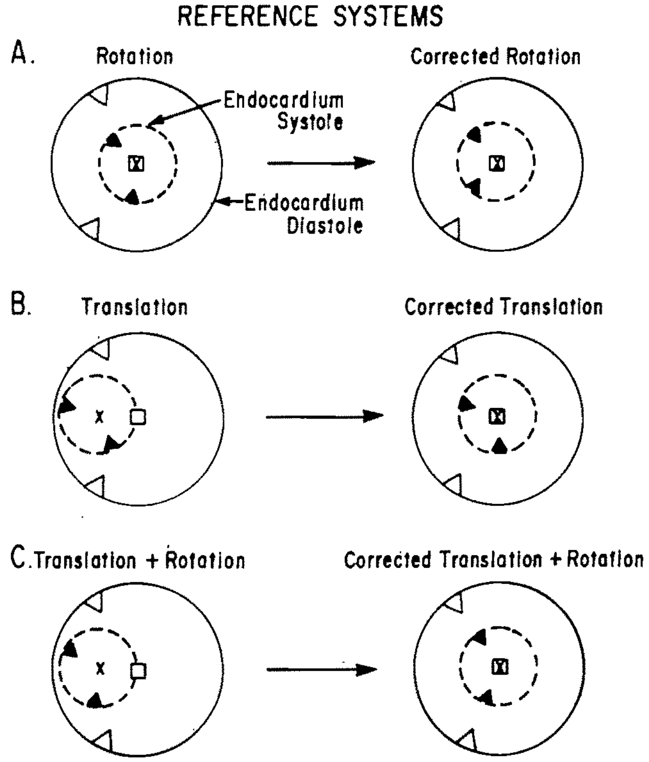

Figure 10. Diagrams of systolic and diastolic endocardial borders, before and after correction by floating axis reference systems.
X, systolic center of mass; □, diastolic center of mass.

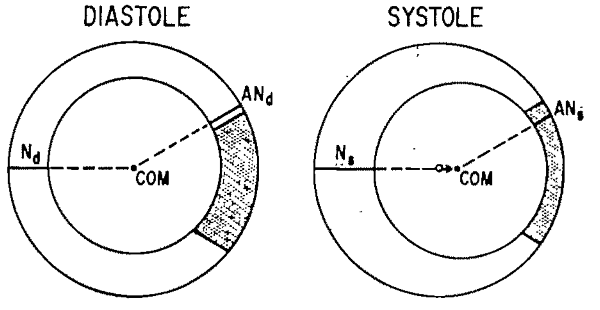

Figure 11. Diagrams of short axis images of the LV wall in diastole and systole, illustrating a center-of-mass analysis for systolic wall thickening.
□, infarct zone; N_d, wall thickness of normal myocardium in diastole; N_s; wall thickness of normal myocardium in systole; AN_d, wall thickness of normal myocardium adjacent to infarct zone in diastole; AN_s, apparent wall thickness of normal myocardium adjacent to infarct zone in systole; COM, center of mass.

Systolic thinning and lengthening of the infarct zone result in a shift of the COM in systole. For analysis of wall thickening, the myocardial circumference is divided into multiple radii. Diastolic and systolic radii are matched by their positions relative to the horizontal. In this way, the diastolic thickness of normal myocardium AN_d can be matched with the thickness AN_s along a radius that falls within the infarct zone.

a percentage of the diastolic circumference. However, dysfunction is identified by comparing radii from the centers of mass in the diastolic and systolic images. Mismatching of radii traversing normal myocardium in diastole with those traversing dysfunctional myocardium in systole occurs because the radii are matched without reference to any myocardial landmark (Fig. 11).

The validity of the different reference methods has been examined by several investigators. Schnittger and co-workers (39) studied 61 subjects with the use of 44 variations of the different reference methods to compare their accuracy in the quantitation of ventricular wall motion. Using a transducer placed on the chest wall, parasternal short axis views at the mitral valve and papillary muscle levels were examined, in addition to an apical four-chamber view. The broad categories of reference methods employed included a fixed external reference, a floating reference correcting for translation, and a floating reference correcting for both translation and rotation. Initially, the LV wall motions of 20 normal subjects were analyzed and plotted to obtain a 95% confidence interval for each of the 44 methods. Subsequently, the wall motions of an additional ten normal and 31 abnormal subjects were compared with the initial group. This study revealed that the absolute values for LV wall motion varied markedly when different reference methods were applied to the same two-dimensional view, and also when the same reference method was applied to different views. Fixed external reference systems generally resulted in wider normal bands than did floating axis methods. For each reference method, the band of normal wall motion was wider for a short axis view at the level of the mitral valve than for one at the papillary muscle level. At the mitral valve level, there was approximately 5 degrees of rotation with systole. The fulcrum of torsion appeared to lie in the body of the left ventricle at the midpapillary muscle level. Translational movement was also found to be minimal at this level. Therefore, a fixed reference analysis method was found to be satisfactory for the short axis view at the papillary muscle level, and in fact was superior to the floating axis reference system for this view. Sensitivity and specificity for normal wall motion at this level were both 95%, clearly superior to the values obtained with other two-dimensional views. It should be noted, however, that the fixed reference analysis applied, while not correcting for translation, matched radii using a myocardial landmark, the papillary muscle, thus correcting for rotation (Fig. 12). Schnittger's results compare well with those of Parisi et al. (40), who, using slightly different methods, reported sensitivity at 95%, specificity at 89%, and predictive accuracy at 92% with a fixed reference analysis of the same short axis view.

Several investigators have examined the advan-

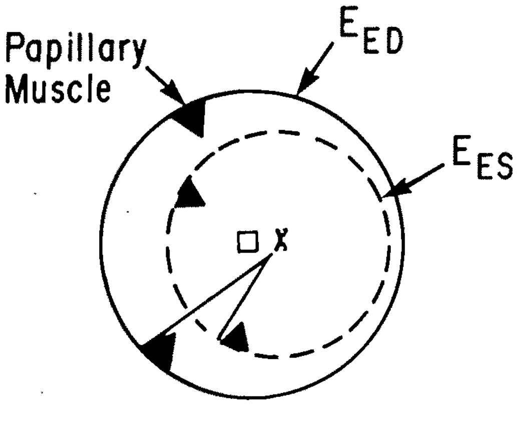

Figure 12. Fixed reference analysis of endocardial motion using the systolic center of mass as the reference point and the papillary muscle as the point of origin for construction of radii on the endocardial border.
E_{ED}, endocardial border at end-diastole; E_{ES}, endocardial border at end-systole; □, center of mass calculated from end-diastolic endocardial border; X, center of mass calculated from end-systolic endocardial border.

tages of dividing the ventricular image into radii vs areas, again usually considering only endocardial borders. Grube et al. (41) found a slight advantage of area over radial methods and Parisi et al. (40) reported predictive accuracy to be better with an area method than with a radial method in conjunction with a fixed reference system. When a floating axis reference system was used, however, there was no difference between radial and area methods. Schnittger et al. (39) found no difference between area and radial methods with image subdivisions up to 45 degrees. In general, 5–30-degree sampling intervals have been recommended.

In contrast to measurements of endocardial wall motion, the measurement of LV wall thickening is not generally subject to errors introduced by translation and rotation of the heart. In using two-dimensional echocardiography, systolic wall thickening of the human LV free wall is seen to vary from 40 to 80% (42–44). In animals, values of 10–30% have been reported (45–47). This apparent discrepancy between human and animal data has been ascribed to the inclusion of compressed trabeculae carneae in the apparent wall thickness as measured by echocardiography. Most animal studies have been done using more direct methods, such as sonomicrometry, with ultrasound crystals attached to epicardium and endocardium.

To validate the echocardiographic measurement of wall thickening, Feneley and Hickie (48) studied 18 normal subjects in whom two-dimensional echocardiograms of the LV short axis were recorded at a midpapillary muscle level. The endo- and epicardial outlines were traced and planimetered to calculate the myocardial cross-sectional areas at end-systole and end-diastole. The investigators reasoned that since myocardial cross-sectional area is a function of wall thickness and wall circumference, overestimation of systolic wall thickening by echocardiography would be expected to involve an overestimation of end-systolic myocardial cross-sectional area relative to end-diastolic cross-sectional area. As a matter of fact, they found a close correlation between the two parameters, with the slope of the regression line approaching unity. They concluded that there is not a significant overestimation of systolic wall thickening by two-dimensional echocardiographic techniques. In this study, systolic wall thickening averaged 50%, exceeding the values in animal studies and in some of the previous studies in humans.

The advantages of measuring systolic wall thickening rather than endocardial motion make it more desirable for quantitative studies. Image quality is not always adequate for delineation of both endocardium and epicardium, but with the recent introduction of improved transducers, and with transesophageal access to the heart, systolic wall thickening is becoming a measureable and useful parameter of cardiac contraction.

Transesophageal two-dimensional echocardiography represents the first practical means by which anesthesiologists can measure and monitor LV dimensions. For a number of years, the Diasonics Corporation has been the sole manufacturer of transesophageal ultrasound probes. However, with the increasing interest in transesophageal echocardiography among both anesthesiologists and cardiologists, other manufacturers have begun to develop transducers for esophageal use. Although the use of transesophageal echocardiography is not yet widespread (because of its expense and unfamiliarity), we and others have found that the technique is simple. We train our residents to use the equipment and interpret the images without the assistance of additional personnel.

Measurement of end-diastolic volume and end-diastolic area (of the short axis image) allows more precise definition of LV preload than does measurement of the central venous pressure or pulmonary artery occluded pressure. From dimension and pressure measurements, it becomes feasible to measure wall stress, which relates to myocardial oxygen consumption.

By considering the dimensions of single segments or regions of the LV wall, regional rather than global wall motion can be assessed. We have seen that abnormalities of regional wall motion are sensitive markers of regional myocardial ischemia. However, it has also become clear that they are not specific for ischemia, as they persist in the face of restored perfusion or infarction. In monitoring for ischemia, the objective involves the serial evaluation of wall motion, since changes occurring over time denote alterations in myocardial perfusion rather than infarction. Several pitfalls in technique, such as gain maladjustments or failure to monitor the same LV segments, can lead to errors in image interpretation.

Qualitative interpretation, although relatively easy to learn, lacks precision, and the full potential of regional wall motion monitoring awaits the development of on-line quantitative measurements. The various off-line computerized analyses each has its limitations. It appears, however, that efforts should be concentrated on the measurement of systolic wall thickening rather than endocardial movement as offering the least potential for error in analysis. With improvements in image quality that allow more precise cardiac definition and advances in computer technology, quantitative measurements will become easier and more timely. It is reasonable to expect that transesophageal echocardiography will supplement the information provided by the electrocardiogram and the pulmonary artery catheter in patients with ischemic heart disease; in some patients, it may entirely obviate the need for a pulmonary artery catheter. For example, patients who require carotid endarterectomy have a high incidence of coronary artery disease but would not merit a pulmonary artery catheter for reasons other than ischemia monitoring. Likewise, patients with a history of coronary vasospasms but good ventricular function could be monitored with transesophageal echocardiography and spared the pulmonary artery catheter.

In addition to the measurement of regional and global cardiac function, the ability to define cardiac anatomy, to detect intracardiac air, and, with Doppler color flow mapping, to map the course of intracardiac blood flow suggests that cardiac imaging has come to stay in anesthetic practice.

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Clinical Reports

Failure of High Frequency Jet Ventilation to Ventilate Patients Adequately during Extracorporeal Shock-Wave Lithotripsy

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High frequency jet ventilation (HFJV) has been used successfully for extracorporeal shock-wave lithotripsy (ESWL) to diminish renal stone movement during general anesthesia and to decrease the number of shocks delivered inadvertently to healthy tissue (1). Although usually uneventful, we present here eight cases out of 407 in which HFJV failed to ventilate patients undergoing ESWL, which necessitated the use of conventional mechanical ventilation (CMV).

Materials and Methods

Four hundred and seven patients were monitored during ESWL by an automated blood pressure cuff (Ohio Sentry), an electrocardiogram, a precordial stethoscope, a pulse oximeter (Nellcor), and a neuromuscular blockade monitor (Professional Instruments NS-2C). A capnograph (Accucap) and a polargraphic-type oxygen analyzer were placed in-line at the junction of the endotracheal tube and the Y-piece of the anesthesia circuit to measure partial pressure of end-tidal carbon dioxide (PET_{CO_2}) and FI_{O_2}, respectively. In all patients anesthetic technique was standardized.

After preoxygenation, anesthesia was induced with intravenous thiopental and fentanyl, 4 μg/kg. A bolus of atracurium, 0.5 mg/kg, was used to facilitate tracheal intubation, which was achieved with a multiple-lumen, Hi-Lo Orotracheal Tube (NCC-Mallinckrodt). After intubation, anesthesia was maintained with 70% N_2O/O_2 and a fentanyl infusion 1–2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, and muscle relaxation was continued with boluses of atracurium as needed. Initially, CMV (tidal volume, 12 ml/kg; frequency, 8–10 breaths/min) was used.

After positioning the patient in the ESWL tank, ventilation was changed to HFJV with a solenoid valve-actuated, time-cycled jet ventilator (Healthdyne Model 300) through a 14-gauge, blunt-needle injector positioned centrally at the proximal port of the endotracheal tube. To maintain PET_{CO_2} below 40 mm Hg at a frequency of 100 breaths/min and 20% inspiratory time (0.12 sec), drive pressure was adjusted between 25 to 40 psi. PET_{CO_2} was measured by turning off the ventilator and providing a large tidal volume (V_T) from the anesthesia bag of the circle system; the patient's exhaled CO_2 was measured using a capnograph. Nitrous oxide and oxygen concentrations were maintained by directing the gases into the ventilator by means of a N_2O/O_2 blender (Bird Products Corporation).

Results

Jet ventilation had to be abandoned in eight patients who developed bronchoconstriction and wheezing when switched from CMV to HFJV in the lithotripter bath. Patients' ages ranged from 37 to 84 yr (seven men, 1 woman). Six patients were classified ASA I or II, and two patients, ASA III. Four patients had a history of cigarette abuse. Preoperative chest x-ray films were normal and none of the patients had a history of asthma. Despite increases in drive pressure to as high as 45 psi, PET_{CO_2} increased to between 45 and 54 mm Hg in these patients and wheezing continued. High frequency jet ventilation was then abandoned and conventional ventilation instituted with the addition of isoflurane into the anesthesia circuit.

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Wheezing ceased and PET_{CO_2} decreased to below 35 mm Hg in all eight cases. No further difficulty with ventilation occurred during the remainder of ESWL.

Discussion

HFJV has been used in patients with acute respiratory failure due to adult respiratory distress syndrome (2,3). However, our experience has been that downstream changes in airway resistance (R_{aw}) may affect alveolar ventilation profoundly during HFJV. Increases in R_{aw} necessarily result in higher peak inflation pressure, as long as all other factors remain constant. Flow entrainment varies inversely with airway pressure (P_{aw}), given the same jet caliber and drive pressure (4,5). P_{aw}, which changes with conditions such as asthma or reactive bronchospasm in airways, is particularly important because downstream resistance tends to stall the flow from the injector, i.e., entrained flow is reduced, and as a consequence, V_T is decreased. Banner and Boysen (6) studied airway resistance and gas entrained with HFJV in a test lung and found that with increased R_{aw}, V_T and gas entrainment decreased to the point where minute ventilation was compromised. This occurrence is probably why HFJV was inadequate in our patients who developed bronchospasm. Carlon et al. (2) reported on 17 patients with respiratory failure who could not be ventilated by conventional means but improved with HFJV. However, one patient with chronic pulmonary disease developed severe bronchospasm upon initiation of HFJV and had to be placed back on CMV. The problem of bronchospasm and adequate ventilation with high respiratory rates (100–200 breaths/min) is not unique to HFJV but has also been reported with high frequency oscillation (HFO) at rates of 900 breaths/min. Crawford and Rehder (7) reported on 67 patients without a history of lung disease, of whom two developed bronchospasm when placed on HFO. These patients had the highest increase in lung volume and the investigators hypothesized that expiratory flow limitations may occur during HFO in recumbent, anesthetized patients. Rossing et al. (8) studied vagotomized dogs given histamine to assess the effect of bronchospasm on HFO. They noted that conductance for CO_2 transport in the lung was less during histamine infusion and reported a marked loss of CO_2 removal during high frequency ventilation in the presence of bronchospasm. Because entrainment of gas is not a feature of HFO, redistribution of more of the V_T to a central airway, termed "shunt compliance," may have decreased the percentage of V_T that actually reached the peripheral gas exchange zone. Although Banner and Boysen (6) concluded that HFJV is contraindicated in patients predisposed to acute bronchospasm, its continued use would be advantageous in patients undergoing ESWL to decrease renal stone excursion, thus warranting attempts to use this mode of ventilation even in patients with a history of bronchospasm.

After these eight cases of bronchoconstriction during anesthesia with fentanyl and N_2O/O_2 in 407 patients, we introduced isoflurane by entrainment through the circle system during HFJV in an additional 200 cases. These 200 patients received fentanyl, N_2O/O_2, and atracurium as the primary anesthetics, with low concentrations of isoflurane entrained into the circuit. We have had no further problems with HFJV in patients who had not wheezed before the induction of anesthesia. The ability to use an inhalational anesthetic during HFJV appears to broaden the spectrum of patients in whom HFJV can be used during ESWL.

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Reversal of Apparent Tolerance to Epidural Morphine by Epidural Methylprednisolone

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Use of epidural narcotics represents a great advance in the management of cancer pain. Unfortunately, tolerance to epidural narcotics frequently develops, necessitating neurodestructive procedures or pharmacologic attempts to "rest" spinal opiate receptors (1). Coombs et al. (2) demonstrated dural thickening surrounding an epidural catheter with a concomitant decrease in cerebrospinal fluid (CSF) morphine concentration resulting in apparent tolerance. We report reversal of apparent epidural morphine tachyphylaxis by the injection of methylprednisolone and lidocaine into the epidural space via a subcutaneous epidural narcotic delivery system.

Case Report

A 69-yr-old male with small cell carcinoma of the lung and metastic involvement of the T-7 vertebral body presented with intractable chest wall and back pain. His pain was unresponsive to nonsteroidal antiinflammatory agents, tricyclic antidepressants, narcotic analgesics, and epidural steroids. After appropriate preimplantation screening (3) an epidurally placed intraspinal narcotic delivery system (INDS) was recommended. In April, 1985, a Radovan reservoir (Heyer Schulte #78635) was implanted with a silastic epidural catheter at the seventh thoracic vertebra to allow for intermittent epidural administration of morphine. The reservoir initially contained 6 mg of morphine dissolved in 10 ml of preservative-free saline that was added every 24 hr. In order to inject the INDS, the subcutaneous reservoir was identified by palpation and the overlying skin was prepared with a providine-iodine solution. A 22-gauge 4 cm needle attached to a syringe containing the morphine solution was advanced through the skin and subcutaneous tissue into the reservoir. The solution was slowly injected and the needle and syringe were removed. The dose of epidural morphine given from the reservoir was increased as needed in 0.5 mg increments.

In September 1985, the patient noted that 8 mg of morphine in 10 ml of preservative free saline provided only 15 hr of pain relief. He also complained of severe burning in the midthoracic area during injection of morphine solution into the reservoir. The burning had increased in severity over the last week. He was afebrile and exhibited no systemic signs of an underlying infection. Examination of the skin overlying the reservoir and catheter showed no sign of infection. The patient was fully ambulatory and denied bowel or bladder symptoms. A computerized tomographic (CT) examination of the thoracic spine was obtained to rule out an occult epidural lesion. The CT scan as well as complete blood count and blood cultures were all negative. The patient's complaint of burning on injection was attributed to inflammatory changes in the epidural space. Methylprednisolone, 40 mg (Depo-Medrol, Upjohn), suspended in 6 ml of 1% lidocaine was injected via the INDS in an effort to relieve the burning on injection. Within 48 hr, injections made into his INDS were no longer painful. Additionally, the patient noted that 8 mg of morphine in 10 ml of preservative-free saline provided 26 hr of pain relief.

The patient was discharged from the hospital and instructed to decrease his dose of epidural morphine by 0.5 mg every 24 hr until the duration of pain relief decreased below 24 hr per injection. Within a week the patient was maintained on a daily injection of 6.5 mg morphine in 10 ml of preservative-free saline. He continued to remain free of the burning on injection.

In February, 1986, the patient noted a gradual return of the burning associated with INDS injection. He was injecting 7.5 mg of morphine in 10 ml of preservative-free saline with only 18–20 hr of pain relief. Physical examination was unchanged and there were no signs of infection. His INDS was reinjected with 40 mg of methylprednisolone suspended in 6 ml of 1% lidocaine. Within 3 days, 6.5 mg of morphine

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in 10 ml of preservative free saline was providing 26 hr of pain relief and the burning on injection of the INDS was gone.

In late March, 1986, the patient noted a sudden drastic reduction of pain relief with 7.5 mg of morphine in 10 ml of preservative-free saline, which now provided only 10 hr of pain relief. In spite of the reduction of pain relief, the patient noted no burning on injection of his INDS. Again, physical examination showed no significant change in his underlying disease or psychological status. We injected his INDS with 6 ml of 1% lidocaine in accordance with protocol (4) to exclude the possibility of delivery system failure. The patient reported prompt relief of his pain with a corresponding sensory deficit that was appropriate for the dose of local anesthetic given thereby indicating that the INDS was functioning. Later that day, his INDS was injected with methylprednisolone, 40 mg, suspended in 6 ml of 1% lidocaine. This injection was repeated the next day, but we were unable to extend the duration of pain relief seen with epidural morphine. The patient began injecting his reservoir every 12 hr with 6.5 mg of morphine in 10 ml of preservative-free saline with excellent pain control.

Discussion

Previous reports have documented the development of rapid tolerance to chronically administered epidural and subarachnoid narcotics (1,2,5–10). Table 1 lists the common causes for inadequate pain control with epidural narcotics. The incidence of inappropriate patient selection as a cause of inadequate control of pain can be reduced by mandatory preimplantation screening (3). So, too, progression of disease or alteration in the patient's physiologic or psychological status must be ruled out. The INDS should be injected with local anesthetic to document that it is functioning properly. If the above factors can be ruled out, one must consider the possibility of the development of a reflex sympathetic dystrophy or drug tolerance. Sympathetically mediated pain may be relieved by injecting the INDS with local anesthetic solutions (8–10). Treatment of spinal opiate receptor tolerance requires neurodestructive procedures or pharmacologic attempts to "rest" the μ-receptors (1,2,5,6,10,11). Spinal μ-receptors may be "rested" by using local anesthetics to provide analgesia until receptor sensitivity returns (11). This "rest" may require more than 2 weeks and may necessitate hospitalization. Alternatively, analgesia may be obtained via δ-receptors by means of intrathecal Da-La2-D-Leu5 enkephalin or an α-2-adrenoceptor agonist such as clonidine (1,2,5,6).

Table 1. Common Causes for Inadequate Pain Control with Chronically Administered Epidural Narcotics

1) Inappropriate patient selection
2) Progression of disease
3) Change in physiologic or psychological status of patient
4) Delivery system failure
5) Development of a reflex sympathetic dystrophy
6) Development of drug tolerance
    a) True spinal opiate receptor tolerance
    b) Pseudotolerance caused by dural thickening restricting transdural diffusion and lower CSF morphine concentrations

An additional consideration in patients with epidural catheters is the possibility that dural thickening alters diffusion kinetics within the epidural space such that systemic absorption is increased and CSF morphine concentrations are lowered (2). We suspect that the initial gradual tolerance that developed in our patient may have been based on dural thickening. Animal studies have documented an inflammatory response to epidural catheters that occurs within 10 days of implantation and ultimately results in a fibrous cocoon surrounding the catheter (12–15). Our patient had a trial of epidural steroids before implantation of the INDS, which may explain the initial 4-month interval before significant tolerance occurred. After injecting the INDS with steroid, another 4-month period without tolerance was noted. The rapid decrease in pain relief in March, 1986 may have been on the basis of true spinal opiate receptor tolerance or irreversible inflammatory changes within the epidural space. The problem of transdural diffusion kinetics may be limited by the subarachnoid placement of catheters. Our experience with subarachnoid catheters has been hampered by the consistent problem of CSF tracking back along the catheter ultimately surrounding the reservoir dome, thus making injection of the reservoir difficult if not impossible. For this reason, we have stopped placing catheters in the subarachnoid space.

Steroids have been injected epidurally for many years with a low incidence of complications (16). When tolerance to epidurally administered morphine develops and there is no change in patient or INDS status, it appears reasonable to consider a trial injection of methylprednisolone and lidocaine prior to neurodestructive procedures or pharmacologic attempts to "rest" the spinal opiate receptors. It would be prudent to test this hypothesis in an animal model to ascertain the ideal timing and dosage of steroid required to limit inflammatory changes.

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Caudal Administration of Morphine Sulfate in Anticoagulated and Thrombocytopenic Patients

Steven D. Waldman, MD, Gary S. Feldstein, MD, Howard J. Waldman, DO, Katherine A. Waldman, BS, and Mark L. Allen, MD

Anticoagulation and profound thrombocytopenia are among the few absolute contraindications to regional anesthesia (1,2). The risk of epidural hematoma is well documented as a rare complication in fully anticoagulated patients given spinal or epidural anesthesia (1,3–6). The issue of the relative safety of regional anesthesia in patients on "minidose" heparin remains unsettled. Should surgery be necessary in an anticoagulated patient, general anesthesia is considered a safer option.

Unfortunately for the patient who is suffering from intractable pain of malignant origin and who is also receiving anticoagulants, the options of techniques for pain relief other than regional anesthesia are more limited.

We report on 37 patients that were fully anticoagulated and 19 patients with profound thrombocytopenia suffering from intractable pain of malignant origin who underwent 336 caudal blocks with morphine sulfate and bupivacaine for pain control, and we review the safety of this approach.

Clinical Observations

All patients were seen at Kansas City Pain Consortium Pain Centers for the evaluation and treatment of intractable lower body pain secondary to malignancy. Thirty-seven patients were being treated with fully effective doses of anticoagulants as defined by a prothrombin time or activated partial thromboplastin time 1.5 or more times above control levels. Twelve patients were receiving continuous heparin infusions. Nineteen patients had profound thrombocytopenia with platelet counts under 50,000/mm^2 secondary to radiation and/or chemotherapy. All patients had received trials of maximal narcotic analgesics and adjunctive drugs parenterally without adequate control of pain. In each case it was felt that discontinuation of the anticoagulants would place the patients at significant risk for thrombotic or embolic sequelae.

Because all conservative options to control pain had been exhausted, a trial of caudally administered morphine sulfate and bupivacaine was felt to represent a reasonable alternative.

Technique of Caudal Block

The patients were placed in the prone position with a pillow placed under the hips. The caudal area was aseptically prepared with Providone-iodine and the sacral hiatus was palpated. A 25-gauge, 1.5-cm needle (or a 25-gauge, 3.8-cm needle in obese patients) was advanced through the sacrococcygeal ligament into the caudal canal. Seven milligrams of morphine sulfate in solution with 20 ml of 0.25% bupivacaine was then injected. After the injection, the needle was withdrawn and gauze sponges were placed over the injection site. The patient was then turned to the supine position with the gauze acting as a pressure dressing. The patients were observed in the Pain Center recovery room for 1 hr during which time the injection site was observed for bleeding and hematoma formation. In no instance did this occur.

On each subsequent visit to the Pain Center, the injection site was observed for evidence of bleeding. The patients were then reevaluated 2 weeks after their last block for any problems related to abnormal bleeding.

Results

Two patients had ecchymotic areas at the injection site. No hematoma formation was noted. In no instance was any change in neurologic status observed that could be attributed to epidural bleeding. Five patients had subsequent placement of an intraspinal

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narcotic delivery system after anticoagulants were discontinued perioperatively. One patient sustained a left-sided cerebral vascular accident after anticoagulants were discontinued for an abdominal exploration.

After observing the safety of this approach in cancer patients, we have expanded its use to allow administration of methylprednisolone and/or bupivacaine in anticoagulated patients suffering from acute and chronic benign pain syndromes of the low back and lower extremities. This technique has proved especially useful in patients with vasospastic disease or in patients after lower extremity vascular surgery when sympathetic blockade is desired.

Discussion

Anticoagulation and profound thrombocytopenia are considered to be absolute contraindications to epidural anesthesia (1,2). Paralysis and bowel or bladder dysfunction may develop rapidly from hematoma formation in the epidural space (5,6). There are numerous reports describing spinal and epidural hematoma in a variety of clinical situations (1,3–17). Hematomas have been reported after spinal and epidural blocks in anticoagulated patients (1,3–6), after epidural anesthesia unassociated with anticoagulants (10), and spontaneously in both anticoagulated and nonanticoagulated patients (11–14). The incidence of epidural bleeding has also been reported to be increased in patients with thrombocytopenia, leukemia, aspirin therapy, and heparin administration (15–17).

Over 4000 cases without permanent neurologic sequelae have been reported where spinal or epidural anesthesia was administered before intraoperative heparinization (18,19). Odoom and Sih (20) reported 1000 cases in which continuous epidural anesthesia was administered without neurologic sequelae to patients receiving preoperative oral anticoagulants. They did not comment on the coagulation profiles at the time of epidural puncture and specifically excluded patients with blood dyscrasias including thrombocytopenia and those receiving heparin or long-term aspirin therapy.

Our clinical experience in 56 patients suggests that caudal epidural blocks administered via a 25-gauge needle in fully anticoagulated patients and in patients with hemostatically significant thrombocytopenia are safe. In no instance were complications secondary to excessive bleeding observed in patients undergoing this treatment. This technique appears to represent a valuable addition to the pain specialist's armamentarium when treating patients with clotting abnormalities.

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Postpartum Uterine Atony after Intravenous Dantrolene

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Dantrolene has been used successfully for prophylaxis and treatment of malignant hyperpyrexia (MH). The relaxant properties of this drug are most prominent on skeletal muscle. Cardiac and intestinal smooth muscle are affected to a lesser degree (1). The action of dantrolene on human uterine muscle has not been described. We report a case of postpartum uterine atony in a patient who received dantrolene during a cesarean section.

Case Report

The patient was a 26-yr-old 100 kg (normal weight 70 kg) nulliparous woman admitted at term because of increasing symptoms of preeclampsia. The patient's niece had a clinical episode of MH. The patient had a muscle biopsy 3 yr previously that showed she was MH susceptible. She had never had any clinical evidence of MH despite undergoing a tonsillectomy during childhood. Her prenatal course was normal until approximately 3 weeks before admission when she developed mild hypertension, proteinuria, and mild hyperreflexia unresponsive to bedrest. On admission she was afebrile, blood pressure was 130/80 mm Hg, and she had mild hyperreflexia. Her coagulation profile and the fetal heart pattern at admission were normal. Approximately 5 hr after admission the patient spontaneously ruptured her membranes. During the next 17 hr, while in prodromal labor, her rectal temperature increased to 38.6°C and her white blood cell count increased to 29,000/μl. Intravenous ampicillin was administered for presumptive chorioamnionitis and rectal acetaminophen suppositories for the fever. She subsequently went into active labor and oral feedings were stopped.

Because her labor failed to progress a cesarean section was decided upon 4 hr later. A hyperbaric 10 mg tetracaine spinal anesthetic was administered and a T-2 level of anesthesia achieved. Supplemental oxygen was delivered at a rate of 5 L/min through a face mask. A healthy term infant was delivered through a low transverse uterine incision. An intravenous infusion of oxytocin after delivery resulted in satisfactory uterine tone. Dantrolene, 220 mg, was then prophylactically administered intravenously; it caused burning at the intravenous site. The patient's temperature was 37.5°C, the arterial pH 7.34, Pa_{CO_2} 26 mm Hg, Pa_{O_2} 181 mm Hg, HCO_3^- 14 mEq/L. Sodium bicarbonate, 135 mEq was infused intravenously and the operation completed. The patient was then taken to the recovery unit with an oxytocin infusion running.

Examination on arrival in the recovery unit revealed an atonic uterus and vaginal bleeding. The total estimated blood loss at this time was 1500 ml. Treatment with uterine massage, intravenous oxytocin, intramuscular methylergonovine, and prostaglandin F_{2a} were unsuccessful. The rectal temperature was 38.1°C, arterial pH 7.32, Pa_{CO_2} 23 mm Hg, Pa_{O_2} 152 mm Hg and the HCO_3^- 13 mEq/L with 5 L/min of supplemental oxygen being administered through a face mask. Arterial blood pressure was 86/40 mm Hg, pulse 150, and the central venous pressure was 10 mm Hg. The hematocrit was 22%. An additional 100 mg of dantrolene and 180 mEq of sodium bicarbonate was administered. Urine was 3+ positive for myoglobin. Over the next 15 min her temperature decreased to 37.7°C. Lactated Ringer's solution, 2000 ml, 5% albumin, 250 ml, fresh frozen plasma, 500 ml, and packed red blood cells, 750 ml were administered. Her coagulation profile at this time was normal. Curettage of the uterus failed to stop the bleeding. Temperature remained below 37.8°C, but arterial blood gases demonstrated a persistent metabolic acidosis requiring additional doses of sodium bicarbonate. She was transferred to the operating room and a hysterectomy was performed under general anesthesia uti-

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lizing a MH designated anesthesia machine and ketamine, pancuronium, N_2O, and fentanyl for the anesthetic. The uterus was found to be atonic. She tolerated the procedure well and made an uneventful recovery. One additional 100 mg dose of dantrolene was administered postoperatively. Blood gas tensions remained within normal limits after the operation.

Discussion

Postpartum hemorrhage, which is defined as blood loss in excess of 750–1000 ml after delivery, occurs in up to 8% of all patients delivered at term (2). In patients who have undergone cesarean section, the most common cause is uterine atony. The incidence of emergency hysterectomy after cesarean section is approximately 0.7%. Emergency hysterectomy for atony is significantly associated with amnionitis, oxytocin augmentation of labor, cesarean section for arrest of labor, preoperative infusion of magnesium sulfate, and increased fetal weight (3).

The action of dantrolene on the human uterus has not been described. Its action on skeletal, cardiac, and intestinal smooth muscle is well known and has been attributed to the prevention of calcium release from the sarcoplasmic reticulum (4). The effects of dantrolene on spontaneous and oxytocin-induced contractions of isolated preparations of guinea pig uterus have been described (5). Dantrolene significantly decreases the frequency and force of oxytocin-induced contractions but transiently increases spontaneously induced contractions in this preparation. The maximal effect develops within 5–10 min after exposure to the drug and continues until the drug is withdrawn. Calcium is ineffective in reversing the effect of dantrolene.

The prophylactic administration of dantrolene both intravenously and orally to MH-susceptible parturients before delivery has been reported (6). The ratio of fetal to maternal venous plasma levels of dantrolene is approximately 0.5 (6). No adverse fetal or maternal effects were reported. Our case differs from those cited, because our maximal blood level was achieved and maintained after delivery of the baby. Subsequent doses of dantrolene were administered because of the presumptive diagnosis of an early MH episode after the cesarean section. At that time she developed a metabolic acidosis and an increased temperature. No respiratory component to the acidosis was present and the acidosis might have been related to a long labor, possibly complicated by chorioamnionitis. However, because an MH episode could not be ruled out it was elected to administer additional dantrolene. Idiopathic uterine atony after cesarean section does occur and our patient may have had mild amnionitis. Although a cause and effect relationship between dantrolene and uterine atony in this case has not been demonstrated, the sequence of events suggests that dantrolene may have contributed to the development of the uterine atony. Immediately after delivery the uterus contracted in response to an oxytocin infusion and it was not atonic until shortly after the loading dose of dantrolene was administered. Note that despite reconstitution of the dantrolene with preservative-free water the patient still experienced burning at the injection site.

Whether pretreatment with dantrolene decreases the incidence of MH episodes under anesthesia when compared with administration of a "safe" anesthetic alone has not been answered. Before delivery it may be prudent to avoid the use of dantrolene because in guinea pig preparations it has been shown to increase spontaneous uterine tone and may therefore have the potential to cause hypertonicity of the uterus. Although further work is needed in this area and in the area of the uterine effects of dantrolene, our case suggests that dantrolene may be associated with a risk of uterine atony. One must weigh this potential complication against the benefit of prophylactic treatment in obstetric patients at the time of labor and delivery.

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Compressed Spectral Array EEG Monitoring during Coronary Bypass Surgery in a Patient with Vertebrobasilar Artery Insufficiency

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Vertebrobasilar insufficiency (VBI) is a common neurologic disorder encountered by anesthesiologists involved in the management of neurovascular and cardiovascular surgery. In the past, unless the services of an electroencephalographer, technician, and a multichanneled EEG unit were available, it was difficult to monitor cerebral function adequately in the operating room. This process has been simplified, however, with the development of the portable processed EEG. It is now possible to routinely monitor cerebral function and to better assure adequate cerebral perfusion during anesthesia. This capability is especially important with VBI because the symptoms appear to be related to changes in blood flow in the vertebrobasilar system.

We describe a case of symptomatic VBI in a patient with severe coronary artery disease in whom urgent coronary artery bypass surgery was necessary. Processed EEG monitoring proved to be important in the anesthetic management of this case.

Case Report

A 59-yr-old male with three-vessel coronary artery disease was scheduled for an urgent coronary artery bypass graft procedure. He had a long history of VBI with symptoms of vertigo, diplopia, and syncope that predictably occurred when he extended his head or turned his head to the left. Evaluation of this condition 6 yr previously included both an angiogram that showed mild atherosclerotic changes in the cerebral vasculature and mild stenosis of the left vertebral artery at its origin, as well as cervical spine films that showed degenerative changes at C4-7; EEG and CT scan were normal. He had previously been treated with coumadin but at the time of surgery was on aspirin therapy. Preoperative physical and neurologic examinations were unremarkable with the exception of a relatively cephalad and anteriorly positioned larynx and VBI symptoms with moderate head extension. Laboratory values were within normal limits and his ECG showed sinus bradycardia with nonspecific ST and T wave changes. Before induction of anesthesia, arterial and pulmonary artery catheters were inserted without difficulty in the left radial artery and right internal jugular vein respectively. In addition, a commercially available EEG monitor with compressed spectral array capability (CSA) was employed (Nicolet-Neurotrac^R EEG Monitor, Nicolet Biomedical Division). This unit presents two channels of EEG-CSA data (left and right cerebral hemispheres) recorded from the placement of five electrodes. These include a reference electrode that is placed in the middle of the forehead close to the hairline; a positive (+) electrode of each channel positioned high on each side of the forehead against the hairline; and the negative (−) electrode of each channel attached immediately above the ear or behind the ear on the mastoid bone. We find that the use of small ECG pad electrodes allows for rapid application and provides an efficient interface between the scalp potentials and the EEG amplifiers. Prior to electrode placement the electrode sites are first cleaned with alcohol and then briskly rubbed with a pumice compound, which reduces the impedance of the stratum corneum of the skin. Symmetrical CSA activity was noted in both hemispheres and was felt to be a normal awake EEG tracing.

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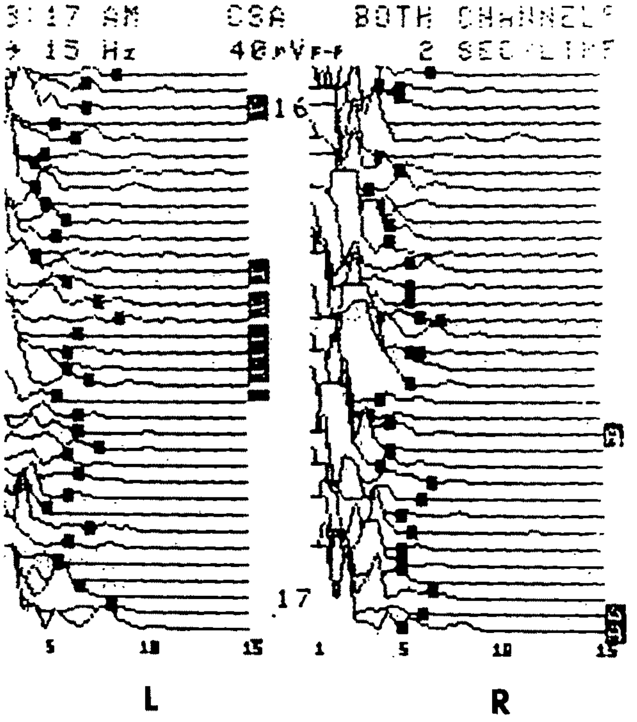

Figure 1. Postinduction compressed spectral array-EEG demonstrating symmetric activity of right and left hemispheres.

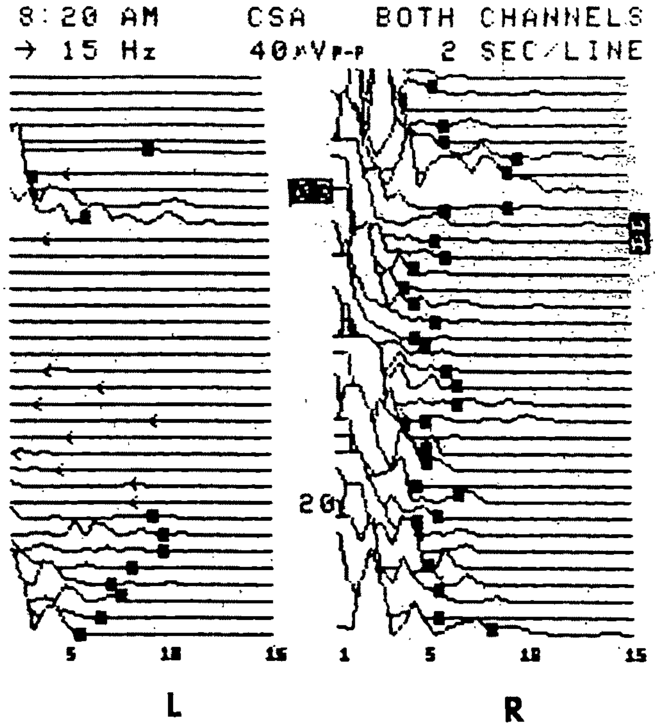

Figure 2. EEG tracing with the head in extension. There is a loss of power and spectral edge in the left hemisphere indicating cerebral ischemia. Normal activity resumes at the end of the tracing.

Anesthesia induction was performed with 50 μg/kg of fentanyl, followed by 0.1 mg/kg of pancuronium bromide, and was associated with a decrease in blood pressure from 125/60 to 105/70 mm Hg. The CSA after induction showed similar activity in both hemispheres with spectral edge (the highest frequency present in the current EEG spectrum) clustered near 6 Hz, indicating an anesthetic state (Fig. 1) (1). Tracheal intubation was attempted with the head in the sniffing position (supported by towels under the occiput) using a MacIntosh blade. Because of the difficult airway anatomy, the initial attempt was unsuccessful. The patient was then ventilated, the towels removed, the head extended slightly, and intubation attempted with a straight blade. This effort was rapidly abandoned, however, due to abrupt loss of left hemispheric CSA activity (Fig. 2) beginning 10 sec after head extension. The head was quickly placed in a neutral position and the CSA returned toward normal in approximately 70 sec. A successful intubation was then performed using the MacIntosh blade with the head remaining in neutral position and with no changes in the CSA. The CSA pattern remained normal until shortly after the onset of cardiopulmonary bypass when again there was loss of left-sided activity. At that time the mean arterial blood pressure was 60 mm Hg. The head was turned slightly to the left resulting in a return to normal CSA activity. The remainder of the operation was uneventful and the patient had no neurologic sequelae in the postoperative period.

Discussion

Vertebrobasilar insufficiency is a common and debilitating neurologic disorder first described in the 1940s (2). One third of all patients with transient ischemic attacks have symptoms referable to the posterior circulation and an incidence of stroke similar to that in carotid disease (3).

Vertebrobasilar insufficiency is a result of occlusive and/or hemodynamic disorders (2–7). Frequently, a combination of these factors leads to an inadequate perfusion pressure in the vertebrobasilar system causing symptoms. The most common single factor is atherosclerotic disease that may occlude the vertebral, basilar, or subclavian arteries at any level. Blood flow may also be affected by anatomic variants such as congenital hypoplasia of a vertebral or posterior communicating artery. Hemodynamic disorders that diminish flow include the reverse flow phenomenon of the subclavian steal syndrome and systemic hypotension. Also, emboli originating from the heart or from atherosclerotic disease may lodge in the more proximal vertebrobasilar system.

Numerous studies document a decrease in vertebral artery blood flow in patients with VBI with movements of the head (8–10). Flexion, extension, and rotation of the head may cause vertebral artery compression secondary to impingement by the bony canal and osteophytes, by atlantoaxial subluxation, or by constriction by the longus colli and scalenus muscles (9). Compression of the vertebral artery can, therefore, occur at any level of the cervical spine. Faris et al. described unilateral vertebral artery occlusion during head turning in 11 of 43 asymptomatic patients (10). Cadaver studies by Toole show that when the head is turned to the side 60°, flow diminishes in the contralateral vertebral artery and ceases altogether at about 80° (8). VBI results in these cases when there is inadequate collateral flow.

Our patient's symptoms of VBI were probably due to vertebral artery occlusion secondary to head rotation and extension. Figure 1 is the postinduction EEG of our patient in the form of a compressed spectral array with symmetric activity (11–13). Figure 2 shows changes indicating ischemia in the left hemisphere with loss of power in all frequencies and loss of spectral edge (13). These changes began 10 sec after extension of the head for intubation. Unfortunately, due to technical problems, the CSA recording in Figure 2 begins approximately 20 sec after the onset of the changes. Intraoperatively, however, the ischemic changes were noted immediately on the visual display, thereby allowing rapid initiation of treatment—in this instance, aborting the intubation and placing the head in neutral position. A normal CSA pattern resulted within 70 sec after onset of ischemic changes. A similar left-sided ischemic CSA pattern developed during cardiopulmonary bypass and normalized after slight turning of the head.

The combination of VBI, coronary artery disease, and difficult airway pose numerous anesthetic problems. This patient demonstrated graphic CSA-EEG changes with head extension indicating a compromised cerebral circulation. Had he been awake, such extension would probably have resulted in VBI symptoms. During anesthesia, the cerebral circulation is vulnerable to head manipulation from the time of induction until full consciousness and motor function are regained by the patient. We believe that CSA-EEG monitoring may well have prevented the development of potentially serious neurologic sequelae in our patient, since it not only allowed for rapid diagnosis of cerebral ischemia, but also enabled us to manipulate the head into a position where the CSA-EEG returned to the normal preinduction baseline. The CSA-EEG is a relatively easy and practical means of routinely monitoring cerebral function intraoperatively, which enables the anesthesiologist to evaluate moment to moment electrophysiologic responses that may indicate early changes in cerebrovascular perfusion. A recent technical review (14) thoroughly evaluates the characteristics and performance of the processed EEG monitors presently available in the USA.

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Postoperative Neurologic Dysfunction Associated with Preoperative Administration of Metoclopramide

Mark S. Scheller, MD, and Kenneth L. Sears, MD

Metoclopramide is a dopamine antagonist that has proven to be useful in the anesthetic management of patients with full stomachs as it is an antiemetic, increases lower esophageal sphincter tone and promotes gastric emptying (1,2). Metoclopramide has also been used to treat nausea associated with chemotherapy as well as chronic regurgitation syndromes (3,4). Toxic reactions to metoclopramide are rare, typically involving the nervous system in what appears to be an extrapyramidal Parkinsonlike disorder (5,6). Administration of even small doses of metoclopramide as a premedicant has been associated with characteristic neurologic abnormalities before the induction of anesthesia (7,8). However, there have been no reports of preoperative administration of metoclopramide being associated with toxicity apparent only postoperatively. This report details such an occurrence.

Case Report

The patient was a 72-yr-old, 75-kg white man who was admitted for coronary artery bypass grafting and replacement of his aortic valve. The patient had been well until 5 yr earlier when he developed stable angina, which had been progressing in severity and frequency. He was otherwise well except for a history of hypertension. He had no history of transient ischemic attacks, stroke, or other neurologic abnormality. The patient did suffer from a documented hiatal hernia and had symptoms of chronic severe gastric regurgitation. Cardiac catheterization demonstrated an aortic valve area of 0.94 cm^2 and a left ventricle to aorta pressure gradient of 36 mm Hg. The coronary arteries had advanced three vessel obstructive disease. The preoperative medications were nifedipine, 10 mg three times a day, isosorbide dinitrate, 40 mg per day, propranolol, 80 mg four times a day, hydrochlorothiazide, 50 mg per day, and oral potassium supplementation. The nifedipine was discontinued 2 days before surgery, but all other medications were continued up until the time of surgery.

The patient was premedicated with metoclopramide, 10 mg orally every 8 hr, beginning in the afternoon the day before surgery for a total of 30 mg. On the morning of surgery the patient was given morphine sulfate, 10 mg, and scopolamine, 0.4 mg intramuscularly, 90 min before induction of anesthesia. After placement of a left radial arterial cannula, pulmonary arterial catheter via the right internal jugular vein, and a large bore intravenous line, anesthesia was induced with fentanyl, and after muscle relaxants, the trachea was intubated and the surgical procedure carried out. Anesthesia was maintained with a fentanyl infusion and paralysis maintained with intermittent boluses of muscle relaxants. The total fentanyl dose was 100 μg/kg. The operation was uneventful with no periods of hypotension. Arterial cross clamp time was 97 min and total cardiopulmonary bypass time was 135 min. Appropriate maneuvers for the removal of air were performed before removal of the cross clamp.

After surgery, the patient was transferred to the intensive care unit. The patient remained cardiovascularly stable throughout the night and was extubated early on the first postoperative day. Upon extubation, the patient was noted to have marked slurring of his speech and unusual upward posturing of his tongue. The consulting neurologist found the patient to be alert and oriented. He followed commands but answered questions only with terse words or phrases and occasionally inappropriately (e.g. hot potatoes instead of hospital). The patient had marked generalized bradykinesis, occasional resting tremor of the right arm, and severe rigidity of all extremities. Strength was normal in the extremities to the extent that they could be evaluated. Deep tendon reflexes

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were increased but symmetrical. Because of the lack of focal findings and the characteristic clinical presentation, an extrapyramidal neurologic disorder was suspected. On reviewing the perioperative medications it was felt that metoclopramide may have been contributing to the clinical picture and diphenhydramine, 50 mg, was administered intramuscularly. Subsequently, the tongue posturing disappeared, although the other abnormalities persisted. A 16-lead EEG was normal and a CT scan of the head done 48 hr postoperatively was unremarkable. The patient was given benztropine mesylate, 2 mg intramuscularly initially, followed by 1 mg per day.

The patient improved gradually over the next few days. He remained oriented and cooperative, but was restless from time to time and required reassurance and physical restraints. By the fifth postoperative day, neurologic examination was normal and the patient felt well. His recall of the previous few days was poor, but he reported feeling "all alone." The remainder of the postoperative course was uneventful and he was discharged on the tenth postoperative day.

Discussion

Neurologic dysfunction after cardiac surgery in adults may occur in up to 20% of patients, depending on clinical and pathological criteria (9,10). It can be divided into two distinct types of abnormalities. The more serious type is CNS infarction, which is typically focal in nature, probably resulting from emboli or other processes causing localized ischemia. Our patient exhibited no true focal abnormality, but rather had rigidity, bradykinesis, and tremor, all signs of an extrapyramidal disorder. Furthermore, the normal CT scan of the head and normal 16-lead EEG argue against an embolic or ischemic basis for the observed neurologic changes in a patient who made a complete clinical recovery. The other type of CNS morbidity seen after cardiac surgery has been termed simply encephalopathy. Breuer et al. reported an incidence of 11.6% in a large series (10). None of their patients had any focal findings, but all were confused and disoriented to some degree. Our patient never appeared confused or disoriented despite his occasional inability to use words correctly. Furthermore, the tongue posturing abated promply with the introduction of diphenhydramine, which is characteristic of drug-induced extrapyramidal disorders.

Extrapyramidal signs and symptoms after administration of metoclopramide are rare, occurring in approximately 1 in 500 patients. They may be manifested by feelings of restlessness (akathisia), facial grimacing, rhythmic protrusion of the tongue, or symmetrical muscular rigidity. The incidence and severity of these side effects increase with the dose and the time course over which the patient is treated (11). Our patient exhibited nearly all of these signs and symptoms. However, even small doses of metoclopramide given preoperatively have been associated with acute neurologic signs and symptoms (7,8).

Our patient was unusual in that the toxic reaction to metoclopramide was not evident until the first postoperative day despite administration of a relatively large cumulative dose (30 mg) beginning 16 hr preoperatively. Because metoclopramide-induced CNS side effects can occur even with small doses, it is unlikely that side effects are associated with specific blood levels. However, it has been shown that hepatic or renal impairment will retard elimination of metoclopramide (12,13). It is possible that hypothermic cardiopulmonary bypass may have influenced the kinetics of the drug, its access to the CNS, or some other aspect of its pharmacology in such a way as to contribute to the manifestation of its toxicity postoperatively.

In summary, preoperative administration of metoclopramide may produce neurologic signs and symptoms in the postoperative period. Anesthetists prescribing metoclopramide should be alert to the possibility of toxicity in the differential diagnosis of neurologic abnormality in the postoperative period.

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Pericardial and Subcutaneous Air after Maxillary Surgery

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Facial, cervical, and thoracic subcutaneous emphysema has been reported after both surgical and dental procedures, or trauma to the upper airway and facial bones, as well as equipment failure (1–3). We report a case in which pericardial air and head and neck subcutaneous emphysema developed after transantral ligation of an internal maxillary artery.

Case Report

A 66-yr-old male with a history of heavy alcohol ingestion and hypertension was admitted because of posterior epistaxis. Therapy included treatment of his arterial hypertension with oral clonidine and hydrochlorthiazide and anterior-posterior nasal packing. After 5 days, the epistaxis persisted, and the patient was brought to the operating room for transantral ligation of the right internal maxillary artery.

On arrival in the operating room, the patient was coughing secondary to the presence of blood dripping down into the posterior oropharynx. He was given 2.5 ml (125 μg) of fentanyl and 1.5 mg of droperidol IV. This premedication made the patient more comfortable and, after preoxygenation, anesthesia was induced intravenously with thiopental, 400 mg, followed by succinylcholine, 120 mg, and cricoid pressure. After an uneventful tracheal intubation, anesthesia was maintained with nitrous oxide, oxygen, and isoflurane. The surgical procedure, transantral ligation of the right internal maxillary artery, was accomplished via a Caldwell–Luc maxillary incision and creation of a nasal antral window for drainage. The surgical procedure was complicated because of difficulty in exposing and visualizing the vessels, which required the creation of an antral window approximately twice the usual size. The procedure was otherwise uneventful, and, at the end of the operation, the patient was breathing spontaneously and was extubated in the operating room. After extubation, the patient's airway became obstructed, presumably because of soft tissue obstruction. An oral airway was inserted and he was given positive pressure bag and mask ventilation. The obstruction cleared easily and the patient was transferred to the recovery room.

On arrival in the recovery room, his airway again became obstructed and positive pressure by mask ventilation was administered by the anesthetist. The obstruction was again felt to be caused by soft tissue in origin. After several minutes of assisted ventilation the airway was deemed to be clear and the patient was awake and able to maintain a clear airway. No note was made of the inspiratory pressures. Subsequently, he was maintained on supplemental 40% oxygen administered via a plastic face mask and his recovery progressed. Thirty minutes after admission to the recovery room, the patient complained that the nasal packing was bothering him and that he had difficulty in breathing. He was again given assistance by the anesthetist with positive pressure ventilation applied via an anesthesia bag and mask. The anesthesiologist was called and upon arrival in the recovery room noted marked swelling of the patient's neck, lower face, and upper chest. The patient became anxious, apprehensive, and combative.

Fearing that the airway might become compromised, the patient was reintubated orally under direct vision using a 7-mm endotracheal tube. At the time, the vocal cords and epiglottis appeared to be pearly white and enlarged. A chest x-ray film showed no pneumothorax but did show massive subcutaneous, mediastinal, and pericardial air (Fig. 1). The patient was transferred to the intensive care unit for further observation. The patient extubated himself 12 hr after admission to the intensive care unit. At that time the airway was clear and reintubation was not necessary. The subcutaneous emphysema resolved without further complication, and the patient made a relatively uneventful recovery. Pericardial air was absent on a chest x-ray film taken 2 days after surgery.

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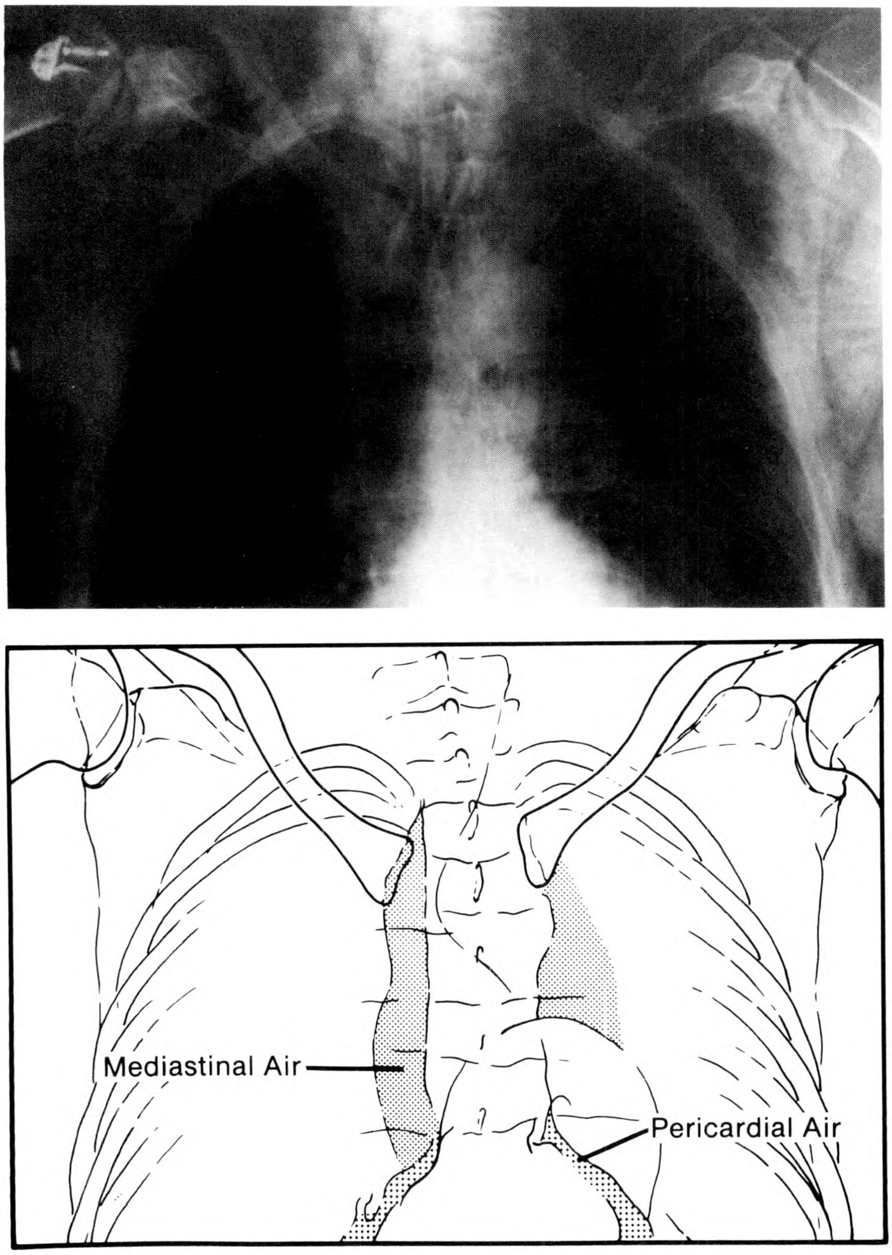

Figure 1. Portable A-P chest x-ray film taken in the recovery room.

Discussion

Subcutaneous emphysema of the face, neck, or mediastinum areas often occurs unexpectedly and without a readily apparent cause. Often it does not have important pathophysiological consequences (4). However, subcutaneous emphysema may be progressive and can lead to both respiratory and circulatory embarrassment. Respiratory compromise may be due to airway obstruction from massive subcutaneous emphysema of the head and neck or decreased pulmonary compliance as a result of a tension pneumothorax. Severe respiratory embarrassment may also occur when air becomes trapped in the pulmonary interstitium, splinting the lungs in an inspiratory position (1). Serious circulatory consequences can develop as a result of increasing tension within the mediastinum, which may reduce cardiac output by a tamponade effect. The occurrence of both circulatory and respiratory compromise has been termed "malignant pneumomediastinum" (5,6).

The presumed route for development of subcutaneous emphysema in the present case is through the disruption of the buccal mucosa and dissection of air along the superficial fascial planes of the face and neck. Air could have easily been forced along this pathway during positive pressure ventilation by bag and mask (7,8). There were probably two distinct causes of airway obstruction in this case. The first obstruction was probably due to soft tissue obstruction secondary to laxity of facial and laryngeal muscles from residual anesthesia. Subcutaneous air was probably introduced at this time and during the subsequent episodes of positive pressure ventilation necessary to clear the airway. The second and third episodes of obstruction were probably due to increasing subcutaneous air and mechanical obstruction of the airway. This etiology was not suspected by the anesthesia team and was not clinically evident until the subcutaneous emphysema became apparent in the recovery room.

Extraalveolar pulmonary air and the planes by which it dissects from one anatomic location to another have been reviewed in several articles; however, none of these articles have described the occurrence of pericardial air after paranasal sinus surgery or after transantral pterygomaxillary fossa surgery (2,4). Because part of this surgical procedure involves the creation of a nasal-antral window for drainage, we postulate that the air was forced back through the nasal antral window through the maxillary sinus and into the pterygomaxillary space. It then dissected retrogradely along the perivascular space following the internal maxillary artery back to the external carotid, to the common carotid, ultimately to the aortic root and to the pericardium. Dissection of air along these perivascular spaces is uncommon after this type of head and neck procedure.

The diagnosis and subsequent treatment of subcutaneous emphysema and mediastinal and pericardial air point out several precautions that should be noted by anesthetists. This case illustrates the danger of using positive pressure mask ventilation after a head and neck procedure in which the perivascular spaces within the airway have been exteriorized, e.g, the pterygomaxillary space via the maxillary sinus. During the perioperative period of head and neck surgery, anesthesia personnel should be alert for changes in pulmonary compliance, circulatory embarrassment, or sudden swelling of the tissues of the head, neck or thoracic regions that may indicate abnormal air entry into the subcutaneous spaces.

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Postoperative Pain Control by Means of Epidural Narcotics in a Patient with Obstructive Sleep Apnea

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Airway obstruction has been reported in patients with sleep apnea after preoperative medication with parenteral diazepam or morphine (1). Presumably, the use of parenteral narcotics for pain control in the postoperative period would also increase the risk of airway obstruction in these patients. We describe the use of epidural narcotics for postoperative pain control in a patient with obstructive sleep apnea.

Case Report

A 68-yr-old 100 kg male was admitted for elective cystoprostatectomy and formation of an ileal conduit for transitional cell carcinoma of the bladder. His history showed chronic obstructive pulmonary disease, obesity, and a diagnosis of obstructive sleep apnea made in 1982. The diagnosis of sleep apnea had been established at another hospital where the patient had presented with incapacitating daytime somnolence. Weight reduction had lessened the complaints, but the patient was still symptomatic. Physical examination revealed no evidence of overt cardiac dysfunction or pulmonary hypertension. Electrocardiogram and other laboratory studies revealed no abnormalities with the exception of mild cardiomegaly noted on the chest roentgenogram. Arterial blood gases (ABG) while breathing room air were Pa_{O_2} 67 mm Hg, Pa_{CO_2} 45 mm Hg, HCO_3^- 29 mEq/L, and pHa 7.42. His medications included albuterol, 4 mg orally three times a day, furosemide, 40 mg daily, and digoxin, 0.25 mg daily.

The patient was given no preoperative sedation. On arrival in the operating room an epidural catheter was placed at the level of L4-5. While the patient was lying supine on the operating room table, before any drugs or oxygen were given, he fell asleep and his airway became obstructed. After several unsuccessful attempts to inhale, the patient awakened, reestablished an adequate airway and appeared to be unaware of what had transpired. This episode was consistent with the history obtained from family members. The patient was then preoxygenated and anesthesia induced with thiamylal, 400 mg IV. Tracheal intubation was facilitated with succinylcholine; an 8.0-mm endotracheal tube was placed with some difficulty secondary to a large amount of redundant pharyngeal tissue. Neuromuscular blockade was initiated with pancuronium, 4 mg IV, and mechanical ventilation begun.

Anesthetic maintenance for the 8.5 hr operation included N_2O, O_2 (60%), and 0.6–2.0% enflurane. Repeated intraoperative analysis of arterial blood samples revealed adequate oxygenation and normocarbia. The intraoperative course was uneventful. At the conclusion of surgery, adequate neuromuscular reversal was achieved with neostigmine, 3.0 mg, and atropine, 1.2 mg intravenously.

The patient was transported to the surgical intensive care unit (SICU) intubated and breathing spontaneously. On arrival in the SICU arterial blood gases with an $F_{I_{O_2}}$ of 0.35 included a Pa_{O_2} of 76 mm Hg, a Pa_{CO_2} of 41 mm Hg, and a pHa of 7.33. Four milligrams of preservative-free morphine were injected through the epidural catheter with minimal change in blood gas tensions: Pa_{O_2} 80 mm Hg, Pa_{CO_2} 43 mm Hg, and pHa 7.34. The morning after surgery the patient's trachea was successfully extubated without problem. The patient received three subsequent 4 mg doses of epidural morphine via the epidural catheter at approximately 18-hr intervals with no significant change in his blood gas tensions or level of conciousness. The epidural morphine afforded excellent pain relief. The patient continued to have his usual symptoms of hypersomnolence with occasional episodes of obstructive apnea. At no time was it necessary to administer a narcotic antagonist or to assist the patient in maintenance of the patency of his airway. The epidural

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catheter was removed on the fourth postoperative day and the patient was transferred to floor care. No further parenteral narcotic analgesics were administered to the patient during his hospital stay and he was discharged 15 days following surgery.

Discussion

The underlying cause of obstructive sleep apnea is felt to be related to a general hypotonia of the dilating muscles of the upper airway, and collapse or invagination of the pharyngeal walls (2). With inspiration and contraction of the diaphragm, a subatmospheric pressure is generated in the airway. This negative pressure is normally opposed by the contraction of pharyngeal muscles, including the genioglossus, tensor palatini, and geniohyoid. Airway obstruction results when the normal balance between these two forces is disturbed (3). The period of apnea is terminated as the stage of sleep becomes light enough to permit reflex opening of the obstructed upper airway. Sedative drugs enhance the reduction in tone of the upper airway musculature during sleep and worsen the severity of the episodes of apnea. Narcotics decrease sensitivity to hypoxia and by this mechanism may decrease the likelihood of arousal.

In patients with mild obstructive sleep apnea reduction of body weight, administration of medroxyprogesterone, supplemental oxygen, or continuous positive airway pressure applied through the nares may be helpful (4). In severe obstructive sleep apnea patency of the upper airway may necessitate surgical intervention. This intervention may consist of removal of tonsillar and adenoid tissue, enlargement of the upper airway aperture by removal of excessive and redundant tissue in the oropharynx (uvulopalatopharyngoplasty), or, if necessary, tracheostomy (5).

The sensitivity of patients with obstructive sleep apnea to sedative drugs and the potential for difficulty in control of the airway is well known (6). Development of respiratory obstruction during induction of anesthesia is usually relieved by elevation of the jaw or insertion of a nasopharyngeal or oral airway. If there is suspicion that tracheal intubation may be difficult, awake intubation under fiberoptic direction is indicated.

Control of postoperative pain with IV morphine can result in obstructive apnea in healthy ASA I or II patients (7). Certainly the risk of such airway problems is not less in patients with obstructive sleep apnea recovering from the effects of general anesthesia. Our patient did not respond well to weight loss and did not have a tracheostomy or other surgical procedure to correct his recurrent obstructive symptoms. For these reasons we elected to use epidural morphine for control of pain and not to subject him to the higher blood levels of morphine that parenteral administration of the same amount of narcotic would almost certainly have produced.

Epidural narcotics have been used with excellent results in control of postoperative pain. However, side effects have been reported, the most serious being the severe depression of ventilatory drive that may occur several hours after injection, although this is an infrequent complication. A recent case report described a patient with central sleep apnea who suffered a respiratory arrest after administration of epidural morphine (8). The etiology of central sleep apnea differs from that of obstructive sleep apnea and is related to a rhythmogenic abnormality in the respiratory center of the brain. In a patient with central sleep apnea the rostral spread of any amount of narcotic in the cerebrospinal fluid could conceivably result in severe respiratory depression.

Ventilatory response to carbon dioxide is decreased after epidural morphine, but the depression is less than that seen with parenteral narcotics (9). In addition, patients may benefit by the more effective restoration of pulmonary function that epidural narcotics allow (10). We felt that epidural narcotics in our patient would provide improved analgesia, less depression of ventilatory drive, and less risk of airway obstruction than parenteral administration of narcotics.

In summary, we have reported the use of epidural narcotics in a patient with known obstructive sleep apnea who underwent intraabdominal surgery. In patients with this disorder who have not yet undergone definitive medical or surgical treatment consideration should be given to the use of epidural narcotics for postoperative pain control. However, if epidural narcotics are used, extended postoperative monitoring of the respiratory system is mandatory in these high risk patients.

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Letters to the Editor

Atrial Fibrillation Associated with Intravenous Fluorescein

To the Editor:

We wish to remind readers of the risk for significant cardiovascular responses associated with the intravenous administration of fluorescein dye. A 56-yr-old man with negative cardiac history and physical examination was taken to the operating room for a fasciocutaneous flap to a wound of the left ankle. Ninety minutes into the procedure, 10 ml fluorescein sodium (100 mg/ml) was administered, at the surgeon's request, over 10 min, and approximately 1 min after the last of the dye was administered, the patient's heart rhythm converted to atrial fibrillation. Cardioversion was eventually required to restore normal sinus rhythm and stabilize vital signs.

Adverse reactions to fluorescein are not rare, usually non-life-threatening, and most frequently take the form of nausea, vomiting, pruritis and urticaria (1–3). There are only a few serious reactions reported; these include myocardial infarction and cardiac arrests, pulmonary edema, and chest pain. This case is the first in which atrial fibrillation has been described. An international survey estimated fatal reactions to fluorescein to be one per 49,557 administrations, and serious reactions, one per 18,020 administrations (4).

The mechanism by which these reactions occur is yet to be elucidated, but allergic reactions or nonspecific histamine releasing mechanisms initiated by the drug or its metabolites must be highly suspect. Histamine has long been known to have effects on cardiac rhythm through several different mechanisms (5) and can easily explain the arrhythmia that developed in our patient.

Mild to moderate adverse reactions to the IV injection of fluorescein is not an uncommon occurrence, but the potential for serious and catastrophic reactions, while less common, certainly exists.

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A Technique to Aid Blind Nasotracheal Intubation

To the Editor:

"Blind" nasotracheal intubation commonly calls for the anesthesiologist to listen for breath sounds at the endotracheal tube end. In this manner, proximity of the tube to the larynx and the phases of respiration can be determined to facilitate the blind intubation.

Often, however, it may be difficult to clearly hear breath sounds coming from the tube. This difficulty occurs when intubation is undertaken in a noisy environment, and when the tidal volume is small, as in children and well-sedated adults. Bending to place one's ear closer to the tube may jeopardize one's ability to simultaneously visualize the patient's head and neck for anatomy and tube location. Furthermore, successful intubation may be heralded not only by a cough, but also by the physician receiving an earful of secretions.

Various devices and techniques have been proposed to aid nasotracheal intubation. These include fiberoptic bronchosopy (1,2), miniature breath sound amplifiers (3), lightwands (4), special endotracheal tubes, stylets (5), humidity in tube and other appliances (6). All these require prior acquisition of equipment and/or skill for their implementations.

The technique of placing the patient end of the anesthesiologist's earmold tubing loosely inside the nasotracheal tube will allow audition of even the shallowest breath sounds. This will spare any necessity of bending over and allow virtually unrestricted positioning for the patient and physician. It requires no special equipment or skill to use. Further, it may limit physician exposure to possible contagion. As the nasotracheal tube approaches and enters the trachea, the breath sounds will increase. If the tube enters the esophagus, breath sounds will markedly diminish if not disappear. In a literal sense, the technique is just like reaching out with the stethoscope to the endotracheal tube.

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Early Blood Patch Recommended

To the Editor:

We read with interest the letter to the editor from Schou and Scherb (1) describing the onset of sagittal sinus thrombosis 4 days after spinal anesthesia complicated by severe postural headache. The close temporal relationship between the dural puncture and the headache and sagittal sinus thrombosis suggests prior low cerebrospinal fluid pressure may represent a common etiology. Low cerebrospinal fluid pressure from leakage of CSF through a dural hole causes descent of the medulla and pons in the cranial cavity in the upright position. This stretches the intracranial dura, resulting in postural headache. Low cerebrospinal fluid pressure has been implicated in more serious complications when other intracranial structures have developed stretch injury. Subdural hematoma (2) and abducens nerve paresis (3) have followed dural puncture and postdural puncture headache. We therefore strongly recommend the use of lumbar epidural blood patch early in the course of the development of postdural puncture headache, in order to try to restore intracranial pressure to normal levels and prevent the onset of more serious sequelae.

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Generalized Grand Mal Seizure after Recovery from Uncomplicated Fentanyl–Etomidate Anesthesia

To the Editor:

We read with interest the report by Goroszeniuk et al. (Anesth Analg 1986;65:979–81) concerning a major motor seizure during the recovery from an uncomplicated fentanyl–etomidate anesthetic. The patient received fentanyl, 150 μg, and etomidate, 20 mg, for the induction of anesthesia prior to cystoscopy and dilation and curettage. She also received additional etomidate to a total dose of 35 mg by the end of the procedure. Three minutes after the surgery she developed a generalized tonic-clonic seizure, which resolved after diazepam, 10 mg, was given. In their discussion, sources (1,2) were cited that describe prolonged myoclonic activity after the administration of etomidate and conclude there was no evidence that these movements were convulsive. In one of these reports (1) no EEG was recorded, and in the other the EEG was uninterpretable because of movement artifact. Grant and Hutchinson (3) reported several cases of seizure activity during prolonged etomidate sedation, but again unfortunately no EEG was recorded.

One of us observed a clinical seizure upon induction of anesthesia with etomidate in a patient with epilepsy. Subsequently our institution reported two patients who, as documented by electrocorticography during the resection of epileptic foci, showed clear activation of epileptiform activity, including one electrographic seizure with the administration of etomidate (4). In another study at our institution, which has been submitted for publication, we have shown that in patients with epilepsy, even small doses of etomidate (6 mg) activate epileptiform activity including spikes, sharp waves, and one electrographic seizure. This effect was seen in 17 of 20 patients (85%) and after 26 of 36 boluses (67%). Since this study was submitted, we have seen one additional generalized tonic-clonic seizure with EEG documentation in response to etomidate. Similarly, Ebrahim et al. (5) have recently published a report showing increased epileptiform activity in 9 of 12 patients (75%) given etomidate during the cortical resection of epileptogenic tissue.

During a study of regional brain glucose utilization in rats, Davis et al. (6) described one rat that showed myoclonic movements after the administration of etomidate. This rat had statistically higher brain glucose metabolism, when compared with other rats that had no seizures, and it can be speculated that the myoclonic movements were in fact a seizure.

We believe that in some patients etomidate may be a convulsant and that Goroszeniuk's patient's seizure most likely was secondary to etomidate. Etomidate may be relatively contraindicated in patients with epilepsy or in patients in whom an increase in the cerebral metabolic rate should be avoided.

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Dural Puncture Headache Suspected, Cortical Vein Thrombosis Diagnosed

To the Editor:

Younker et al. (1) in their interesting article about cortical vein thrombosis and the obstetric anesthesiologist reminded me of a basic problem confronting the obstetric anesthesiologist, namely, the differential diagnosis of headache and neckache in the peripartum period.

A healthy, well-hydrated 31-yr-old woman received epidural anesthesia for repeat cesarean section. Because of anatomical and technical problems, the first epidural catheter placement was unsuccessful and had to be redone. The patient's operative and postoperative courses were uncomplicated for the first 16 hr, but she then reported posterior headache and neckache brought on by assuming an upright position and relieved by reclining. Dural puncture headache was suspected by her physician. Oral fluids were encouraged, and bed rest and analgesics were prescribed. She was seen at 24 and 48 hr. There was no neck stiffness. By 72 hr she had only minimal headache and felt well otherwise. Later that day she developed numbness of the right side followed by three generalized motor seizures. She was treated with diazepam, phenytoin, and dexamethasone. The seizures were controlled, but the patient remained aphasic and hemiplegic on the right for several days. CT scan of the head showed edema of the left hemisphere. Coagulation studies were normal. Spinal fluid examination 5 days after delivery revealed xanthochromia. Cortical vein thrombosis was diagnosed. Dysphasia and right hemiparesis improved with therapy over twenty months.

It was my reasoning initially that 1) the patient could have had a dural puncture during placement of the epidural catheter without spinal fluid being seen; 2) the headache brought on by assuming the upright posture was compatible with a spinal headache (I have seen several patients with neckache only), and 3) other causes of headache such as infectious processes and subarachmoid hemorrhage would be extremely unlikely. Conservative therapeutic measures were begun, and epidural blood patch therapy was discussed.

The patient's headache improved, fortuitously reducing the need for an epidural blood patch, thereby avoiding an association of the procedure with the catastrophic neurological injury produced by the cortical vein thrombosis. Since attending physicians may not have sufficient reason to consider subarachnoid hemorrhage as a cause for peripartum headache, conservative therapy and observation for a few days before giving an epidural blood patch to patients with suspected dural puncture headaches may be wisest.

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What is the Normal Work of Breathing?

To the Editor:

In a recent article, Bolder et al. (Anesth Analg 1986;65: 853–9) demonstrate that the work of breathing through an endotracheal tube increases when respiratory rate or tidal volume is increased or when the endotracheal tube diameter is decreased. However, there is confusion as to whether breathing through an 8.0-mm endotracheal tube actually doubles the work of breathing, as the authors state.

In the discussion, the authors state, on the one hand, that 0.07 Watts is the normal work of breathing. On the other hand, in their experiment, using an 8.0-mm endotracheal tube with a tidal volume of 500 ml and a respiratory rate of 20, they calculate the work of breathing to be 0.07 Watts. How, then, does the endotracheal tube increase the work of breathing at all, much less double it?

Another bit of confusion arises in Figure 3 of the article. This graph is intended to show that, at any of the experimental combinations of rate and tidal volume, the work of breathing decreases as the radius of the endotracheal tube increases. The graph would be correctly drawn if the radius of the endotracheal tube were plotted on the x axis. However, the x axis is labeled 1 over the radius in which case the graph lines should be slanted in the opposite direction. I suspect that this was merely a mislabeling by the authors.

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pH Adjustment of Chloroprocaine Solutions

To the Editor:

The article by DiFazio et al. regarding the pH adjustment of lidocaine solutions used for epidural anesthesia was most interesting and enlightening (1). Chloroprocaine (Nesacaine®) has a comparatively low pH, and pH adjustment might accelerate the onset of action. Table 1 shows results of the addition of 0.5 mEq aliquots of sodium bicarbonate to 30 ml stock 3% chloroprocaine of two different lot numbers, at room temperature. The pH was measured with a Radiometer PHM84 pH meter immediately after each aliquot of bicarbonate was added and mixed. It is obvious that the addition of a small amount of $NaHCO_3$ appreciably increases the pH of the resulting solution. In the clinical use of 3% chloroprocaine without $NaHCO_3$ added for cesarean section, adequate surgical anesthesia, in my experience, is usually obtained within 14–15 min after injection. On several recent occasions, I have used pH-adjusted 3% chloroprocaine, adding 1 mEq $NaHCO_3$ to 30 ml 3% chloroprocaine, and surgical anesthesia was achieved in 6–8 min. With urgent cesarean sections under epidural anesthesia, this shortening of onset time has been most advantageous.

It should be noted that epinephrine in a solution of pH over 7.0 has a markedly reduced life and effectiveness, and any solution prepared by pH adjustment should be used immediately, especially if epinephrine is added. I should also note that we have added a small amount of bicarbonate to 0.5% bupivacaine solution, which caused precipitation. I suggest extreme caution if pH adjustment of bupivacaine solutions is attempted.

Table 1. pH of 3% 2-Chloroprocaine with Added Bicarbonate[a]

	pH
Control	3.84
0.5 mEq	6.72
1.0 mEq	6.99
1.5 mEq	7.15

Note: Above mEqs (=1 ml) were added to 30 ml 3% 2-Chloroprocaine.
[a]Mean of two samples, two lot numbers.

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Temperature of IV Solutions

To the Editor:

The study of delivery temperatures of heated and cooled intravenous solutions by Norman et al. (1) yields helpful clinical information. It prompts me to report an alternative and fast method of warming solutions that I have used for several years.

Microwave ovens, which are commonly used in US hospital staff lounges for heating food, work equally well for the warming of IV fluids.

Using an Amana "Radarange" at the "full-power" setting, I have found that the following internal temperatures (measured with a Hi-Lo temp, Model 8200, Sensortek Inc., Clifton, NJ) are reliably achieved in 1-L plastic bottles of lactated Ringer's solution (American McGaw, American Hospital Supply Corp., Irvine CA):

Time in oven	Fluid temperature achieved
2 min	45°C
3 min	54°C
4 min	56°C

The 2-min warming is ideal for rapid fluid-loading before spinal or epidural anesthesia for cesarean sections. The warm fluid feels comfortable to the patient and avoids the shivering so commonly seen when large volumes of room-temperature fluid are infused. Others may find this method useful when warming cabinets are either unavailable or unstocked.

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Reference

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Book Reviews

Hemotherapy in Childhood and Adolescence

N.L.C. Luban and J Kolins, eds. Arlington, VA: American Association of Blood Banks, 1985, 105 pp, $24.00.

The foreword states that this monograph is intended to bring together "different aspects of transfusion that are unique to the older pediatric patients." As in any multiauthored text, there is an uneven coverage of the topics. An objective measurement of the unevenness is to compare the 15 pages devoted to blood ordering, a subject of great interest to anesthesiologists, to the 38 pages devoted to hemoglobinopathies. While this might be a measure of the complexity of the two subjects, comparison of the bibliographies of these two chapters reveals only four of the 16 references in the former and 66 of the 125 references in the latter published since 1980.

The chapter on hemoglobinopathies is outstanding, combining a comprehensive review of the literature and the author's personal experience and providing succinct guidelines. The chapter on mechanical devices in pediatric transfusion is unique and equally comprehensive, providing information on such diverse subjects as autotransfusion with placental blood in the infant (not necessarily among the "older pediatric patients") and a wide variety of infusion pumps that have been used to administer blood or its components in pediatrics. This chapter concludes with the lament that "the pediatric patient should not continue to be the 'orphan' of the blood banking industry."

In summary, this monograph contains much information that will be of interest to anesthesiologists, especially those who care for pediatric patients on a regular basis. For the price, this reviewer considers the monograph a bargain.

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Anaphylactic Reactions in Anesthesia and Intensive Care

Jerrold H. Levy. Stoneham, MA: Butterworths, 1986, 173 pp, $22.95.

Anesthesiologists frequently expose patients to risk by administering potential antigens such as anesthetic agents, blood products, and antibiotics. We also care for patients who receive other potential antigens such as radiocontrast media and chymopapain. An anaphylactic reaction to these substances is not only a life-threatening complication for the patient, but a frightening event for the anesthesiologist as well. When we suspect a reaction has occurred we are immediately faced with questions: is it an anaphylactic or an anaphylactoid reaction, what is the offending agent, how do I confirm the diagnosis, what is the best treatment, and how can I prevent my patient from having further reactions?

Dr. Levy's *Anaphylactic Reactions in Anesthesia and Intensive Care* is a refreshing (by virtue of it being written by a single author), small textbook that provides answers to our questions. Divided into two major sections and 13 chapters, it leads the reader in a logical progression through the basic mechanisms underlying anaphylaxis, to the manifestations of anaphylaxis, to a practical discussion of methods for treatment, and finally, to a brief discussion of prophylactic measures.

A few of the many good aspects of the book deserve special mention. For example, the presentation and writing style make for easy reading and understanding. There were no obvious printing errors. The inclusion of representative cases and a detailed description of protocols make the book of considerable use to the clinician. The protocol for management of anaphylaxis in Table 9.1 should be copied and kept in one's anesthesia machine. The bibliography is up-to-date, with all 432 references conveniently located at the end of the book. There are only a few figures, but those that are included are well-done and support statements made in the text.

Despite the overall excellence of the book, it has a few minor problems. In chapters 10 and 11, which discuss care of the patient after the initial resuscitation from an anaphylactic reaction, the author attempts to provide a practical plan for subsequent management of the patient. However, the approach to some issues is a bit too cursory. For example, one paragraph is alotted to a discussion of the importance of cardiac output determinations, yet no mention is made of how to utilize the data. In Table 11.2, it is suggested that PEEP be adjusted to achieve a PaO_2 of 80–100 with an $FI_{O_2} < 0.6$, yet no mention is made of the concept of "best PEEP" or the potential cardiovascular risks associated with applying PEEP. Finally, the subject of weaning from mechanical ventilation is considered in only one page.

The attempt to make this portion of the book useful to the clinician is admirable, yet the discussion is too superficial.

Determining the cause of an anaphylactic reaction is a challenging problem, and Levy offers a variety of useful tests. Nevertheless, a few omissions were noted. The protocol for testing sensitivity to local anesthetics, outlined in Table 5.2, provides no details regarding technique (the reader must refer to the original reference for details). Also, there is no mention that in vitro tests for drug allergy fail to detect sensitivity to drug metabolites (which may be the causative antigen).

In conclusion, Levy has done an excellent job. The few problems with the book are relatively minor. Overall, it is well-written, well-organized, informative, and a unique, welcome addition to the anesthesia literature. This reviewer will not go so far as to recommend that all anesthesiologists purchase the book, but I will recommend that it be purchased for every anesthesia library where it can be readily accessed. Anesthesiologists must be well-informed when encountering a patient with a severe anaphylactic or anaphylactoid reaction. Levy's book is an ideal source for that information.

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A Practice of Anesthesia for Infants and Children

J.F. Ryan, I.D. Todres, C.J. Coté and N. Goudsouzian, eds. Orlando, FL: Grune & Stratton, Inc., 1986, 314 pp, $67.50.

This book presents a tremendous amount of knowledge on each page. The Pediatric Anesthesia Group of the Massachusetts General Hospital has been very successful in providing an in-depth presentation of the most pertinent aspects of pediatric anesthesia in a text that remains didactic and easy to read. The book is divided into 24 chapters averaging 15–20 pages for each presented topic and readily allows the digestion of each in one short session. This book will be very useful to students and residents encountering pediatric anesthesia for the first time, as well as to persons involved in lecturing on these subjects, as a ready reference for the rapid and comprehensive recall of the topics to be presented. The compact nature of the book does not carry the discussion into the last esoteric detail but liberally utilizes references instead. A pragmatic and scientific presentation results, and the definite need to consider the psychological needs of the child and family in administering anesthesia is not neglected.

Fundamental themes such as pediatic pharmacology, airway, temperature regulation, and fluid and blood management are presented, as well as topics like neonatal and pediatric emergencies, controlled hypotension, burn therapy, and malignant hyperthermia. The presentations on croup and epiglottitis are excellent. The book is not without printing errors, and this is readily evident in the table of contents which lists chapters 17–24 as starting on the wrong pages. Another error is the apparent combination of Preface and Acknowledgement and printing of both in identical fashion, except for the title on back-to-back pages.

Frequently pediatric drug doses are given throughout the book and as useful tables inside the rear cover. Only one incorrect dosage was noted in the text, and care should be taken to verify unfamiliar dosage regimens from any textbook. The presentation of calcium flux during muscle contractions in Fig. 20-1 is also erronious and misleading, most likely due to printing error. Such shortcomings detract insignificantly, and I highly recommend this book to anyone interested in the many topics presented.

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Regional Opioids in Anesthesiology and Pain Management

U.H. Sjostand and N. Rawal, eds. Boston: Little Brown and Co., 1986, 135 pp, $24.00 (single issue), $53.00 (per annum).

This 24th volume of the International Anesthesiology Clinics is written and edited by experts experienced in the material presented. The volume is a relatively short, concise review of a rapidly expanding field, and in large part presents an excellent overview of this material. Many of the chapters provide an excellent starting point for clinicians interested in venturing into this area of patient care. In particular, the chapters on pharmacodynamics and pharmacokinetics and the one on chronic pain management are very practical "must reading" for such clinicians. Several other chapters are also well-written but are limited by their brevity. For instance, the chapter on opiate receptor mechanisms was well-done, but suffers from its briefness and its dependence on graphs and tables while ignoring anatomic or diagrammatic illustrations of pathways and interactions. In addition, the chapter on current views of opiate receptors in anesthesia is very interesting and well-done but suffers from brevity. The chapter centers heavily on analgesia and volatile agents, but does not delve into using high-dose opiates for general anesthesia.

Despite the above minor criticisms, this volume of International Anesthesiology Clinics is an excellent one and very nicely supplements the review article on epidural and intrathecal opiates by Cousins and Mather in *Anesthesiology* 1984;61:276–310. I would heartily recommend this volume to all interested in understanding and using this analgesic modality.

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Neonatal Anaesthesia and Perioperative Care

D.J. Hatch and E. Sumner. Baltimore: Edward Arnold, 1986, 271 pp, $59.50.

The last 20 years have seen revolutionary advances in the treatment of neonates, increasing the need for expert anesthetic care as more sick babies come to surgery. None of the current anesthesia texts (including *Pediatric Anesthesia* texts) adequately discuss the care of these patients and their unusual medical and surgical diseases. This monograph, which is Volume 5 of the *Current Topics in Anesthesia Series,* attempts to fill this void.

The text includes six chapters: "Perinatal Physiology," "The Surgical Neonate," "Anaesthesia—Basic Principles," "Anaesthesia—Specific Conditions," "Postoperative Care," and "Resusitation of the Newborn." There are also three useful appendicies: the first is a nine-page table of syndromes and medical conditions with the associated anesthetic considerations; the second is a drug dosage guide, and the third is a table of normal laboratory values. This second edition differs little from the first (copyright 1981). It contains updated references, and the chapters are expanded.

The authors of this text have again narrowly missed the opportunity to produce a classic reference text on this subject. All the ingredients are there, but the proper emphasis is not. An example is the chapter on physiology. Rather than highlighting key principles, then focusing on their implications for anesthetic management, this chapter is an abbreviated version of material well-treated in current neonatology and physiology texts. The same mistake is made in the long and difficult chapter on postoperative management. The authors seem to want to summarize all of neonatology and pediatric intensive care in 40 pages.

This reviewer was most disappointed with the generalized discussions found in the chapter entitled "Anaesthesia—Specific Conditions." A tightly referenced presentation of the published experience in the surgical and anesthetic management of these conditions with a critique and annotation by the authors would have been more useful to an interested anesthesiologist preparing to manage an infant with one of the problems discussed.

Despite reservations, this reviewer recommends this book to anyone with a special interest in pediatric anesthesia. Much information included here is not found elsewhere in the anesthesia literature. Additionally, the volume is well-indexed, the appendices are helpful, and the references for further reading will significantly reduce the amount of time one will spend in the library researching some topics. This is a good book that falls just short of being a great one.

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Cardiac Anaesthesia: Problems and Innovations

S. DeLange, P.J. Hennis, and D. Kettler, eds. Dordrecht, The Netherlands: Martinus Nijhoff Publishers, 1986, 200 pp, $52.50.

This book is the latest in a series of twelve Dutch monographs on "Developments in Critical Care Medicine and Anesthesiology" published by Martinus Nijhoff and contains contributions by its Dutch and German editors, as well as anesthesiologists from Italy, Austria, Sweden, and the US. All submissions are in English, with the exception of one figure legend in German, but there are many misspellings, typographical errors, and grammatical mistakes. The typeface and spacing change with each chapter.

The preface introduces the text as a compilation of invited papers presented at the first European symposium on "Recent Advances in Cardiac Anesthesia" held May 9–10, 1985, in Leiden, The Netherlands. The European Association of Cardiothoracic Anaesthesiologists was actually organized during this symposium to provide its membership with a forum for "free exchange of new ideas and methods [in cardiac anesthesia] in Europe [as in the US]."

Despite multiple authors, there is little redundancy or repetition in the 21 papers or "chapters" dealing with preoperative preparation, elective anesthetic management, intraoperative monitoring, and anesthetic management of surgical emergencies in cardiac patients. Particularly noteworthy are the submissions on maintenance of preoperative medications, preoperative evaluation of mitral valve disease, invasive monitoring, anesthetic techniques, intraoperative metabolic balance, and management of cardiac surgical emergencies. Unfortunately, most submissions read like outlines for the oral presentation that they really were, and the figures are inserted in the text as slides in a lecture. Other minor weaknesses include failure to identify all abbreviations, occasional improper scientific units, a few figures without legends, and the classification of amrinone as a direct sympathomimetic, rather than as a cardiac phosphodiesterase inhibitor.

The three American submissions have been included among the noteworthy. These submissions also distinguish themselves for the book's longest chapter (16 pages), longest sentence (9 lines, 92 words), and most extensive, if not most current, list of references (44). In contradistinction to these submissions, the final four chapters by Dutch authors on anesthetic management of cardiac emergencies (cardiac tamponade, leaking prosthetic valves, massive pulmonary embolism, ruptured coronary artery following angioplasty) average 4.5 pages, have few misspellings, and contain practical clinical information with clear dosages and simple monitoring choices for emergency use. Finally, the index is comprehensive, but is not cross-referenced, and is full of abbreviations.

This book may have been better (and cheaper) conceived as a meeting syllabus or journal supplement. Despite the few shortcomings that could be predicted in a work of its nature, this book provides us with good insight into the organization and clinical commitment of our European colleagues in cardiac anesthesia. Overall, this book is current, but contains little new information, and would best serve practicing anesthesiologists who care primarily for adult patients undergoing cardiac surgery.

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Practical Management of Pain

R. Prithvi Raj, ed. Chicago: Yearbook Medical Publishers, 1986, 956 pp, $125.00.

This is an impressive collection of original contributions in the area of chronic pain, its history, diagnosis, and management. In keeping with the multidisciplinary approach to the treatment of chronic pain syndromes fathered by J.J. Bonica, the 45 contributors to this text are from widely varied fields within the health care system.

That this book represents the state-of-the-art can been seen at a glance through the table of contents. All conceivable aspects of pain management are addressed in this book. References to the chapters are recent, representing work published through 1983. In keeping with the diversity of opinion in the field, the authors hail from all parts of the western world.

In spite of the division of the book into six parts, there is a redundancy of presentation indicative of the lack of simple answers (or simple questions, for that matter) in the field of chronic pain. Much of what we think, or think we know, is a synthesis of work done in many areas. This book is an outstanding example of the diversity of our knowledge. The editing was apparently accomplished without offending any of the contributors.

The consecutive reading of chapters in this book is impaired by a general lack of consensus from one author to the next in discussions of the same topic. Although this diversity of opinion is in keeping with a style first presented in other great books compiled on the subject of pain, it occurs here under the guise of a text.

As a reference for the library, the pain clinic, and for fellows studying with the intention to direct a pain center later, this book is essential. It is broad in scope, and represents the most complete source book in the field of chronic pain written to date.

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Advances in Anesthesia

Robert K. Stoelting, Paul G. Barash, and James Gallagher, eds. Chicago: Yearbook Medical Publishers, 1986, 403 pp, $55.95.

In this third of the recent series of monographs by this publisher on advances in the field of anesthesiology dating back to 1983, 17 authors from 11 institutions across the US present updates on topics pertinent to providing modern anesthesia and intensive care. Each chapter is carefully written and extensively referenced. A detailed index facilitates ready access to specific clinical problems and data. None of the chapters in this third volume appeared in the two previous volumes. Unfortunately, those readers anxious to secure earlier volumes in this series for their collections will be dismayed to find volume one is out of print. Because each chapter is so complete and extensive, the reviewer finds it difficult to cite outstanding chapters.

This volume, like other review texts, suffers from the lack of really up-to-date information, as judged by the references. Less than 2% of the references were published in 1985 and none in 1986. The chapter on allergy contains no information about reactions to antibiotics, which we may unwittingly produce as we administer antibiotics, sometimes hurriedly, at the request of surgeons.

On balance this volume will prove thought-provoking and informative to residents preparing for examinations, faculty needing thorough reviews of certain topics, and practitioners needing concise information about clinical problems expected with tomorrow's challenging cases or today's surprising complications. The organization of the material facilitates a review of problem areas for the reader in contrast to the very consise reporting of recent papers as found in the *Yearbook of Anesthesia.* Probably, each approach has its virtues and drawbacks.

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Cardiotonic Drugs: A Clinical Survey

Carl V. Leier, ed. New York: Marcel Dekker, Inc., 1986, 312 pp, $69.75.

Over the past several decades, an increasing number of inotropic drugs have become available for the treatment of congestive heart failure. This multiauthored book reviews exclusively the group of cardiotonic drugs best known as positive inotropes, emphasizing the numerous studies investigating this group of drugs and their clinical application in the management of patients with congestive heart failure. *Cardiotonic Drugs* is well-written, and the presentation of the information is comprehensive and concise. Each chapter is extensively and currently referenced (references through 1985 are cited). The figures and diagrams within the book are clear and easily understood.

The initial chapter covers in extensive detail the indices utilized to determine the inotropic state of the ventricle. The clinically relevant discussion of the pitfalls of current techniques used to measure inotropy is well-presented. Parentally administered positive inotropic drugs in the acute clinical settings are addressed. Little information, however, is included on their use to facilitate weaning from cardiopulmonary bypass and immediate post bypass support. The chapter on digitalis is elaborately written, providing an overview of the pathophysiologic basis for the use of digitalis in the treatment of heart failure in humans. Pharmacokinetics and pharmacodynamic effects of digitalis are concisely and thoroughly presented.

Subsequent chapters focus on the following classes of positive inotropes: nonparental sympathomimetics, phosphodiesterase inhibitors, and bipyridine derivatives. The final chapter of the book introduces endogenous positive inotropic substances and discusses their potential role in man's cardiovascular function.

The editor states in the preface that this book is intended "to provide to basic and clinical scientists and practicing physicians a comprehensive current treatise on the group of cardioactive drugs generally referred to as positive inotropes." This reviewer believes the authors have accomplished their stated purpose.

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The 1986 Year Book of Anesthesia
MEDICASSETTE™ Anesthesia, Volume 1, Numbers 1, 2, 3

Ronald D. Miller, Robert R. Kirby, Gerard W. Ostheimer, Lawrence J. Saidman, and Robert K. Stoelting, eds.
Chicago: Year Book Medical Publishers, 1986, 387 pp, $44.95; 6 tapes/year, $75.00.

The 1986 *Year Book of Anesthesia* is the latest edition of a classic series reviewing that segment of medical literature relevant to anesthesia practice. The five editors have abstracted and commented on 310 articles published between September 1984 and October 1985 in 70 journals. The breadth of material covered is evidenced by inclusion of a sole article from each of 32 journals, including a report on "The Effect of Acupuncture on Experimentally Induced Itch," published in *Acta Dermato-Venereologica* (Stockholm). Such breadth does not sacrifice depth of coverage: 27% of articles appeared in *Anesthesia and Analgesia* or *Anesthesiology*, with those 85 articles divided evenly between the two publications.

If this compendium could serve as a sensitive and specific tool for capturing the literature important to anesthesiologists, one could substitute its use for a personal reading of the literature. Alas, since each person defines importance differently, no such subset can satisfy everyone. Of course, one must trust the editors to select the major developments for presentation. Since the editors form a group of distinguished senior academicians experienced in this task and worthy of this trust, *The Year Book of Anesthesia* comes close to the goal of sensitivity. About specificity there can be no doubt: it is lacking, and appropriately so! The several extraneous reports of marginal interest (e.g., "Does Surgery Attract Students Who Are More Resistant to Stress?") lend color and diversion to sustain the reader through an otherwise continually intense reading experience. The 118 illustrations, all reproduced from the original publications, display study results and are essential to an understanding of the articles reported. New chapters in this year's book are titled "Anesthestic Techniques," "Potassium, Calcium and Magnesium," "Coagulation," and "Aspiration Pneumonitis." Each of the five articles in the electrolyte chapter could and should have been incorporated in other book chapters. In contrast, the 11 articles on coagulation form a cohesive unit worthy of a distinct grouping.

The individual editors have distinct styles. One chooses controversial articles and expounds his personal approach prolifically in the opinion section. Another writes terse philosophic comments, like "Etomidate still appears to be a drug in search of a use." Rather than detract from this compendium, the individual styles enhance its value. However, this reviewer wishes the senior editor had taken more liberty in other stylistic matters: the phrase "This is a fascinating study" appears so often in the reviewers' comments that it becomes a cliché. Each of the editors often includes his opinion of the clinical implications of the abstracted work.

For the most part, the articles abstracted are original investigations. I was pleased to see several clinically important case reports reviewed as well. Often the comment section contains a reference to another related article. At the end of a few chapters, a list of appropriate review articles appear. It is unfortunate that the editors found only six such review articles worthy of such mention. On the whole, *The 1986 Year Book of Anesthesia* is a handsome, compact volume of value to the busy clinician and the academically-based physician alike. It is a ready reference to the year's literature of importance to anesthesiologists.

In the MEDICASSETTE™ tape series, two professional narrators read abstracts and opinions of 16 articles. The format is similar to that of the *Year Book*. Each cassette comes with a list of the articles including names and addresses for reprint requests. A cassette binder (not evaluated) is available at extra cost ($9.95). Each tape opens with a pleasing 15-second segment of "traveling" music. After this, Dr. Miller offers introductory remarks consisting of the titles of some of the articles that follow. For each article, one narrator reads the abstract and the other reads the editor's comment. After each review, a brass fanfare is played prior to beginning the next article. Eight articles are reviewed on each side of the cassette.

MEDICASSETTE™ seems to contain a greater percentage of articles of direct clinical relevance than the *Year Book*, although one can learn about ventilatory patterns during normal sleep and about lung neutrophils in respiratory distress syndrome as well. The illustrations so useful in the *Year Book* are necessarily absent in the MEDICASSETTE™ series. However, one does not notice this very much: presumably articles selected for MEDICASSETTE™ did not require graphic accompaniment.

This listener found the professional narration awkward. The enunciation was indeed precise. However the narrators' unfamiliarity with anesthesia terminology greatly hindered effective communication. Problems included mispronunciations ("kee-ta-meen" for ketamine), improper pauses within a sentence that changed its meaning (did the text have commas placed correctly?), and subtleties of inflection that disclose a speaker uncomfortable with his topic. This is not to imply that narration by the editors would produce an overall superior tape.

The traveling music suggested to me that one could listen to the tape while driving to and from work. When I tried this, I discovered I would have to relocate to make this successful: it is virtually impossible to concentrate on the narration while driving in city traffic. My colleagues who commute via long stretches of monotonous highway may find much better results.

The MEDICASSETTE® series seems attractive to those physicians who can't find the time to read even the *Year Book*. This listener believes the audio medium is ill-suited for its task and would rate MEDICASSETTE® a second choice to the *Year Book*.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Cervero F, Morrison JFB, eds. Progress in Brain Research, Visceral Section, Volume 67. Amsterdam, The Netherlands: Elsevier, Biomedical Press, 1986, 324 pp, $255.00.

DeKornfeld TJ, ed. Anesthesiology. New York, NY: Medical Examination Publishing Company, 1986, 560 pp, $33.95.

Garratty G, ed. Current Concepts in Transfusion Therapy. Arlington, VA: Amer Assoc Blood Banks, 1985, 323 pp, $34.00.

Hindman BJ, ed. Neurological and Psychological Complications of Surgery and Anesthesia. Boston: Little Brown & Co., 1986, 284 pp, $18.00.

Howland WS, Rooney SM, Goldiner PL, eds. Manual of Anesthesia in Cancer Care. New York: Churchill Livingstone, 1986, 321 pp, $27.00.

Jones RM, ed. Current European Anesthesiology, The Yearbook of the European Academy of Anesthesiology. New York: John Wiley & Sons, 1986, 308 pp, $48.00.

Katz J. Steward DJ, eds. Anesthesia and Uncommon Pediatric Diseases. Philadelphia: WB Saunders Co., 1987, 560 pp, $65.00.

Kittle CF, ed. Current Controversies in Thoracic Surgery. Philadelphia: WB Saunders, 1986, 304 pp, $49.95.

McQueen MJ. SI Units. Burlington, Ontario, Canada: Simole Consultants Ltd, 1982, 204 pp, $8.00.

Merriam-Webster's Medical Desk Dictionary. Springfield, MA: Merriam-Webster, Inc. 1986, 790 pp, $18.95.

Morrison JD, Mirakhur RK, Craig HL. Anaesthesia for Eye, Ear, Nose, and Throat Surgery, 2nd edition. New York, NY: Churchill Livingstone, 1985, 210 pp, $37.50.

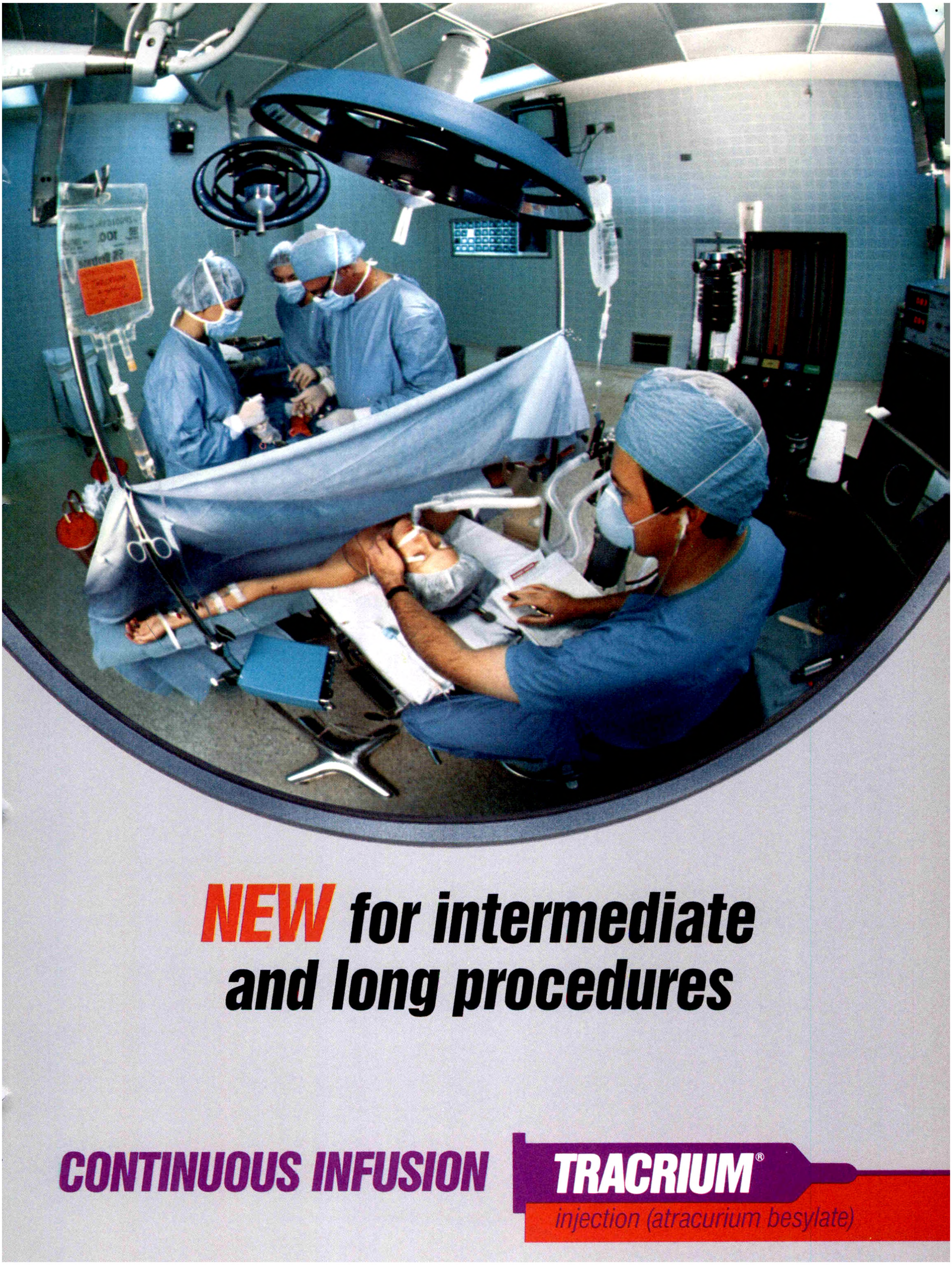
Peter B, Kraiker C. Bibliographie: Psycho(physio)logische Aspekte und Behandlungen von Schmerz. W. Germany: University of Munich, 1986, 106 pp, $8.00.

Shnider SM, Levinson G, eds. Anesthesia for Obstetrics, 2nd edition. Baltimore: Williams and Wilkins, 1987, 566 pp, $65.95.

Stoeckel H, ed. Quantitation, Modelling and Control in Anaesthesia. Stuttgart: Georg Thieme Verlag, 1986, 310 pp, $50.20.

Swedlow DB, Raphaely RC, eds. Cardiovascular Problems in Pediatric Critical Care. New York: Churchill Livingstone, 1986, 311 pp, $42.00.

Varkey GP. Anesthetic Consideration for Craniotomy in Awake Patients. Boston: Little Brown & Co., 1986 (Volume 24, No. 3, Intl. Anesth. Clin. Series), 190 pp, $53.00.



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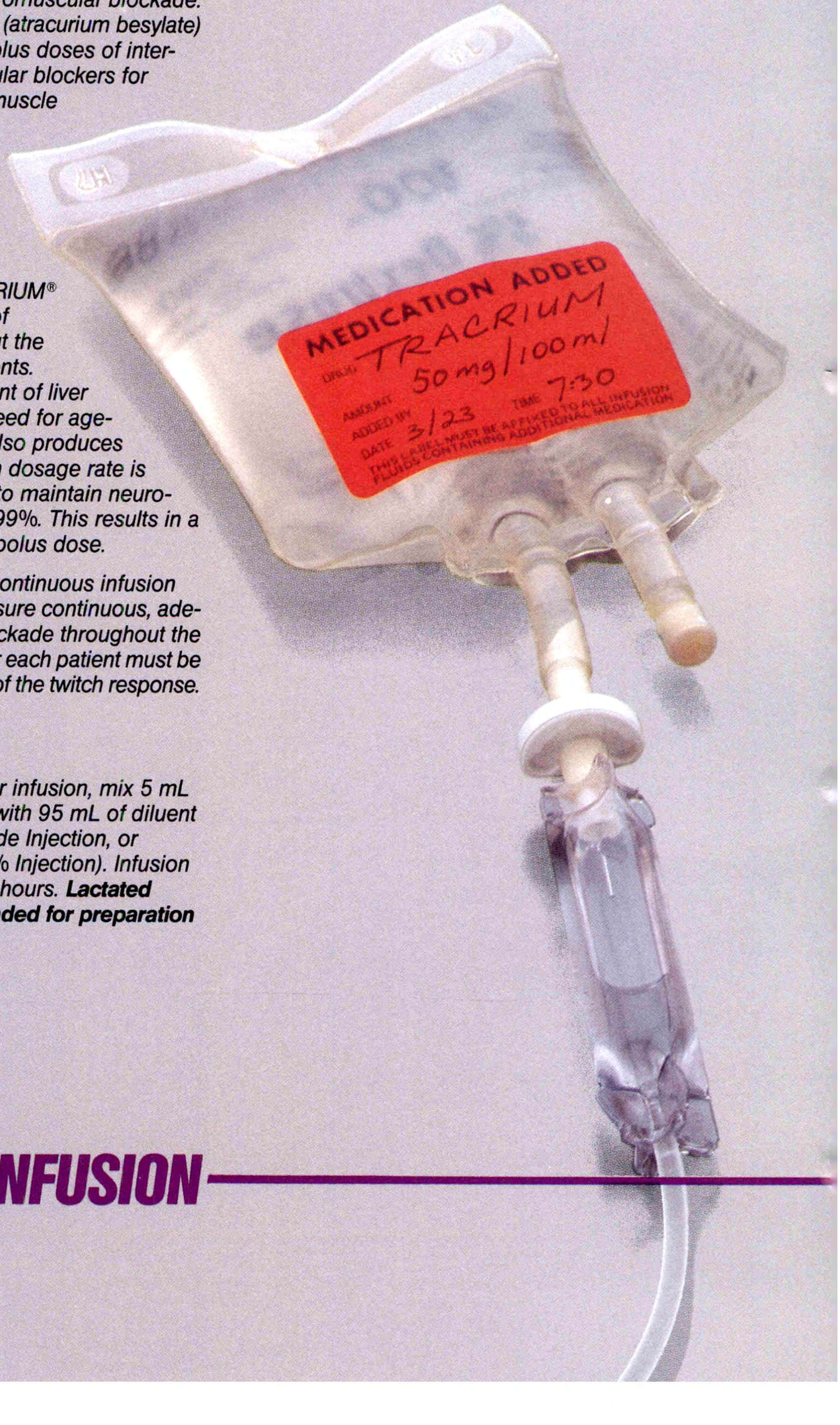
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Initial loading dose: *Administer an initial bolus dose of 0.3-0.5 mg/kg (approximately 21-35 mg in a 70 kg adult).*

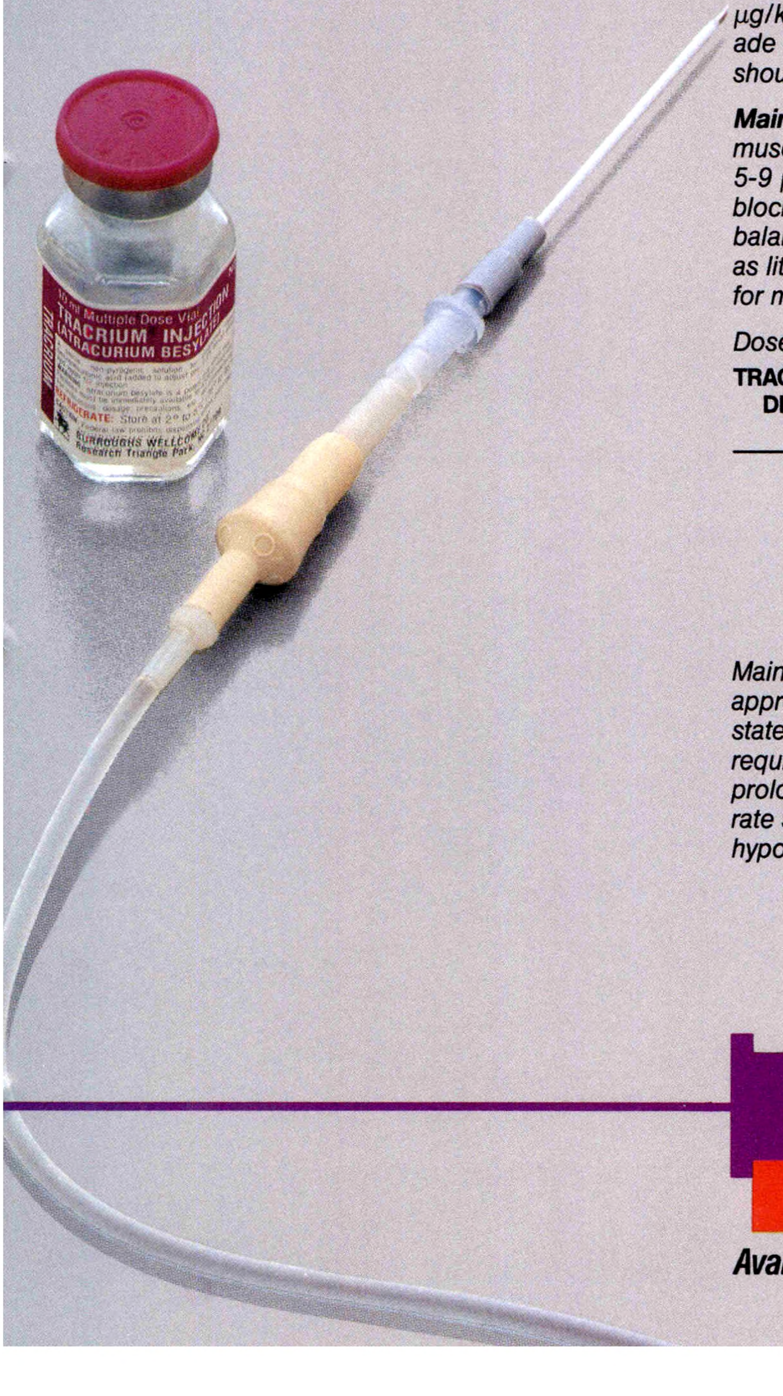
Initial infusion dose: *Infuse TRACRIUM® at a rate of 9-10 µg/kg/min to maintain 89-99% neuromuscular blockade until steady-state relaxation is achieved. Dosage should be titrated to the individual patient's needs.*

Maintenance infusion dose: *Once steady-state neuromuscular blockade is achieved, an infusion rate of 5-9 µg/kg/min is adequate to maintain continuous blockade in the 89-99% range for most patients under balanced anesthesia. Occasional patients may require as little as 2 µg/kg/min, or as much as 15 µg/kg/min for maintenance.*

Dose Calculations:

TRACRIUM INFUSION DELIVERY RATE µg/kg/min	**INFUSION DELIVERY RATE 0.5 mg/mL SOLUTION mL/kg/min**	**mL/kg/hr**
5	0.010	0.60
6	0.012	0.72
7	0.014	0.84
8	0.016	0.96
9	0.018	1.08
10	0.020	1.20

Maintenance infusion rates should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane; smaller reductions are required for halothane. Hypothermia (25°C-28°C) can prolong the effect of surgical relaxation, so infusion rate should be reduced by about one-half during the hypothermic period.



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Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:
Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients with 0% change in heart rate. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequent reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Bolus Doses for Intubation and Maintenance of Neuromuscular Blockade:
Adults: A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular blockade generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Tracrium in these patients, and no specific dosage adjustments can be recommended. No Tracrium dosage adjustments are required for patients with renal disease.

Use by Infusion: After administration of a recommended initial bolus dose of Tracrium (0.3 to 0.5 mg/kg), a diluted solution of Tracrium can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures. Infusion of Tracrium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of Tracrium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 µg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 µg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia.

The neuromuscular blocking effect of Tracrium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Tracrium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of Tracrium infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane. In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of Tracrium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of Tracrium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Tracrium infusion solutions may be prepared by admixing Tracrium Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Spontaneous degradation of Tracrium has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Tracrium for infusion.

The amount of infusion solution required per minute will depend upon the concentration of Tracrium in the infusion solution and the dose of Tracrium desired (see table).

Tracrium (atracurium besylate)—Rates of Infusion for Concentrations of 0.2 and 0.5 mg/ml

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (ml/kg/min)	
	0.2 mg/ml*	0.5 mg/ml**
5	0.025	0.010
6	0.030	0.012
7	0.035	0.014
8	0.040	0.016
9	0.045	0.018
10	0.050	0.020

*2 ml of 1% (10 mg/ml) Tracrium Injection added to 98 ml of diluent
**5 ml of 1% (10 mg/ml) Tracrium Injection added to 95 ml of diluent

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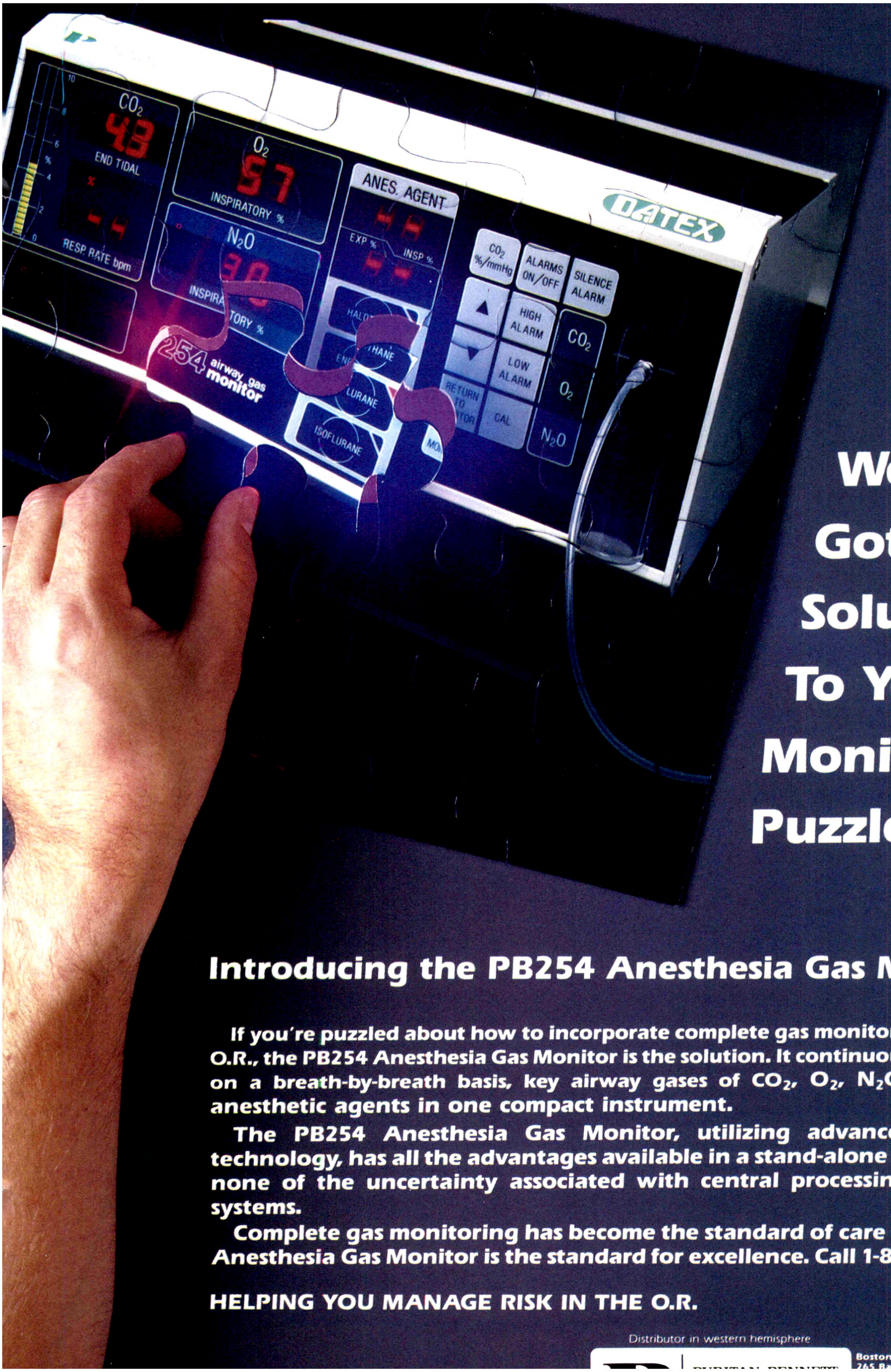

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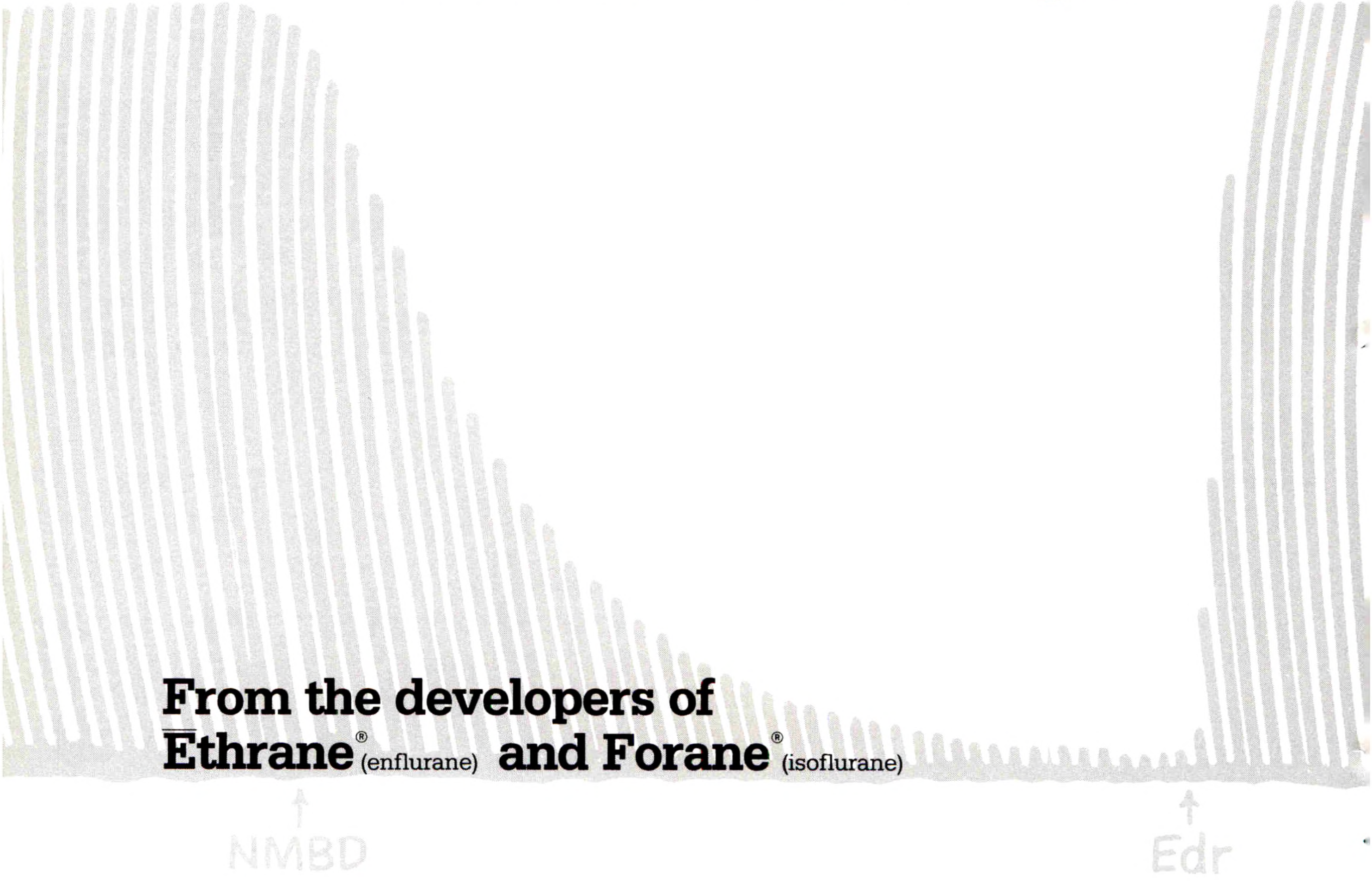

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- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]
- **May be the preferred reversal agent for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

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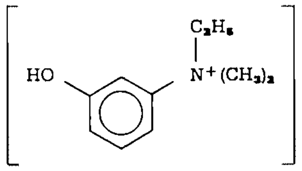
Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anti-cholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilised.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

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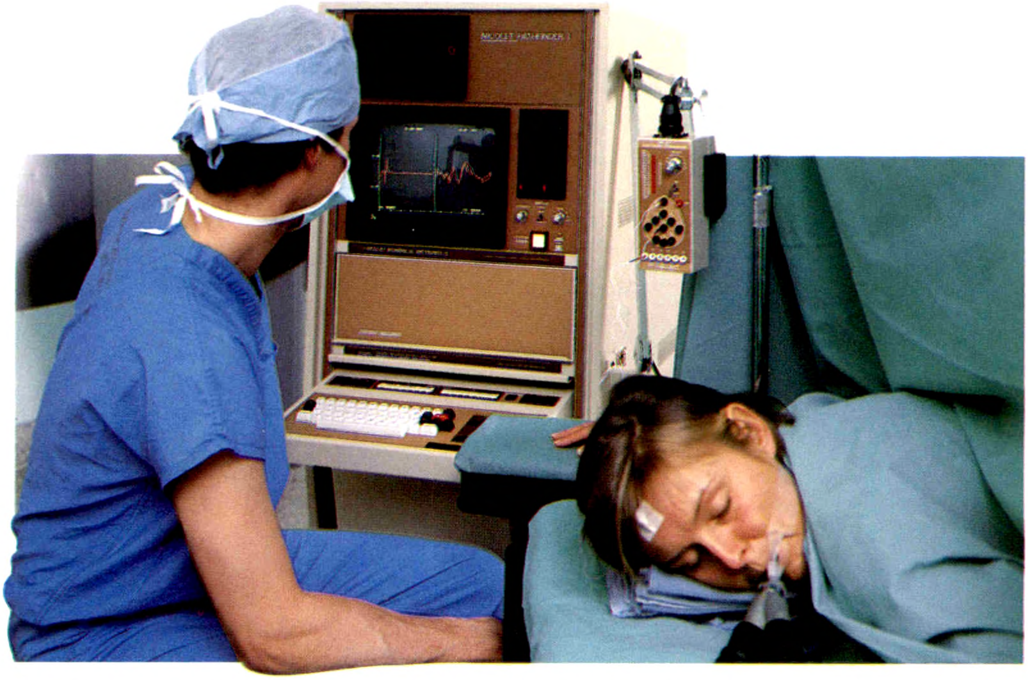

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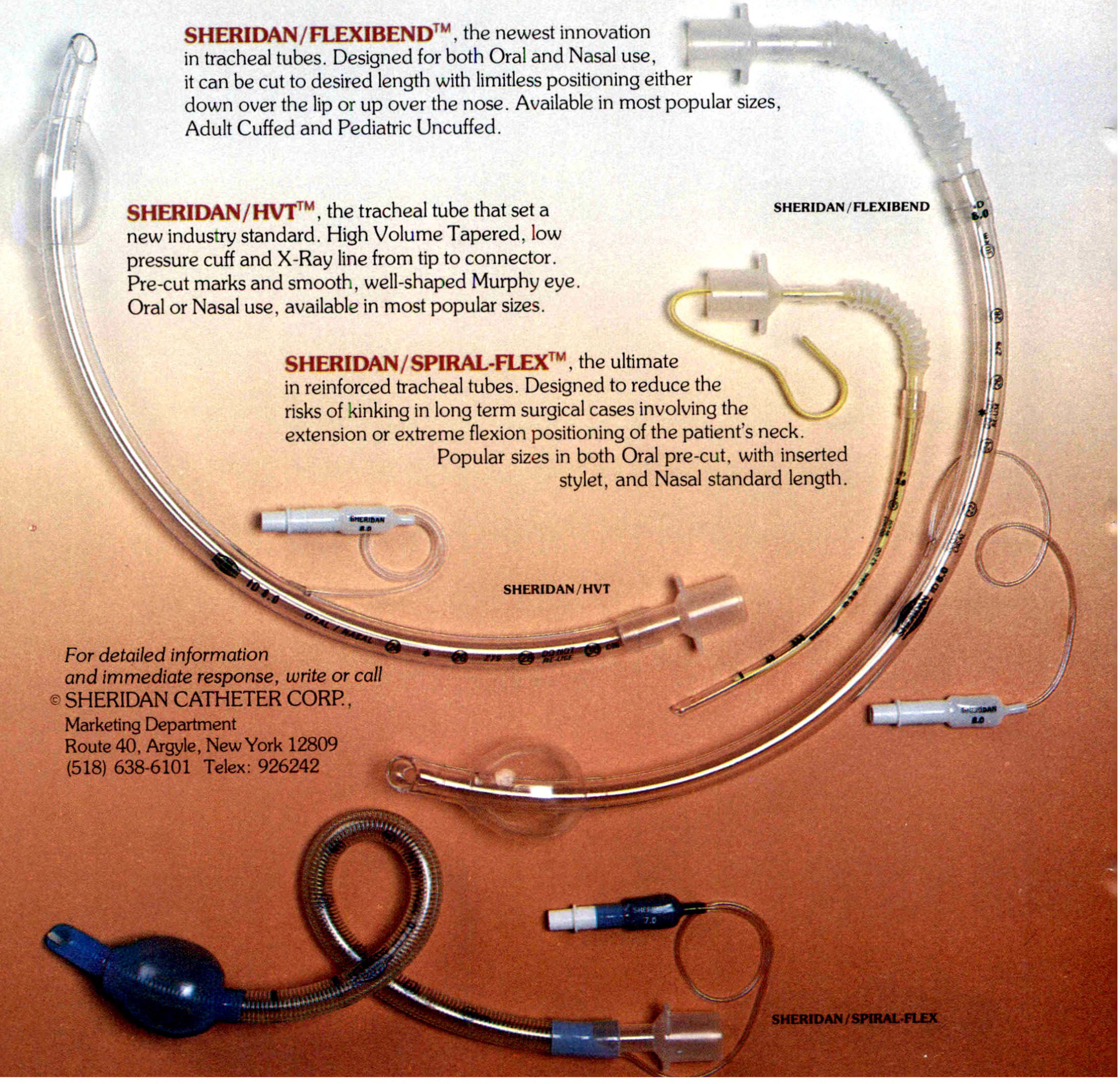

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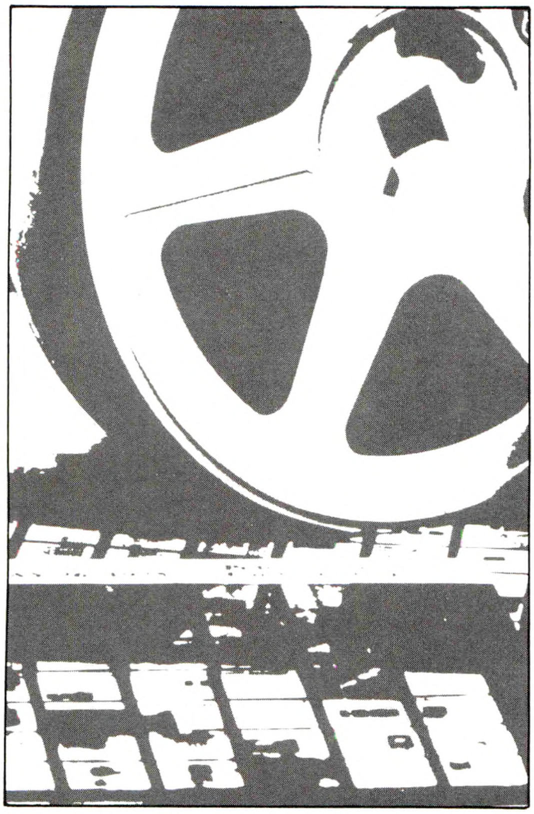

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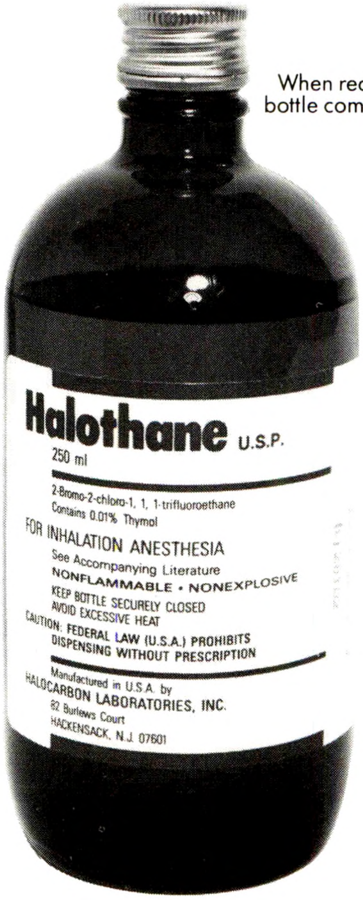
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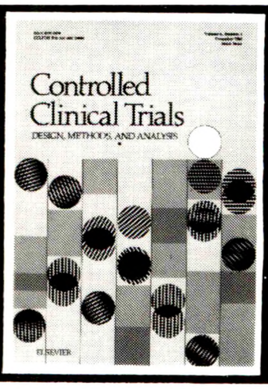

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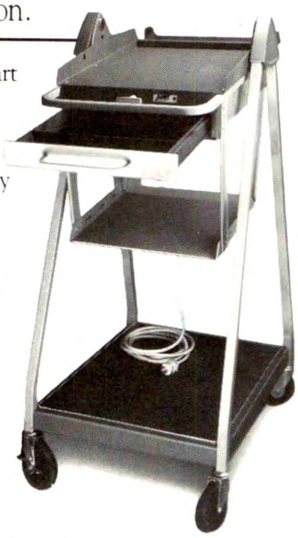

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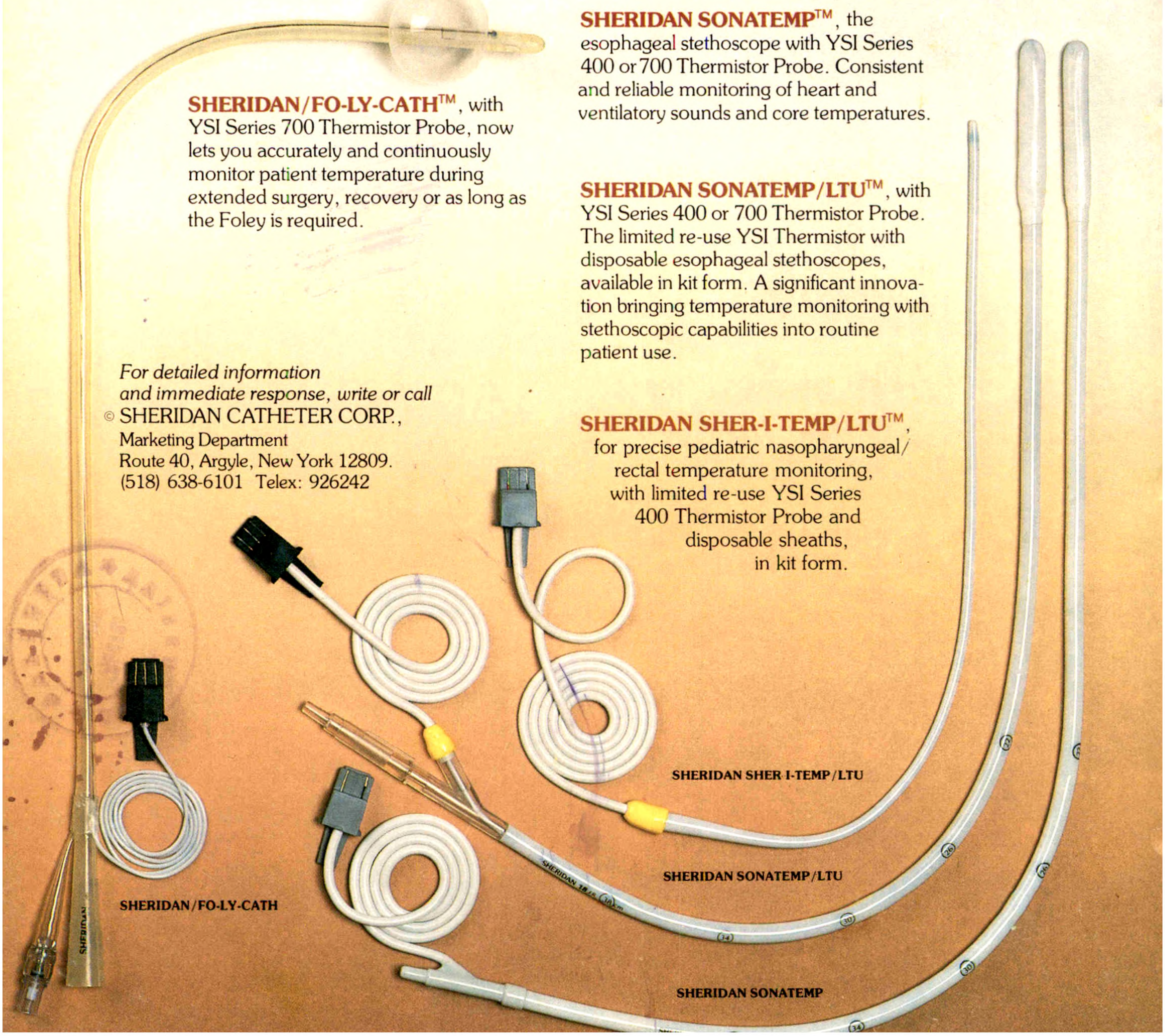

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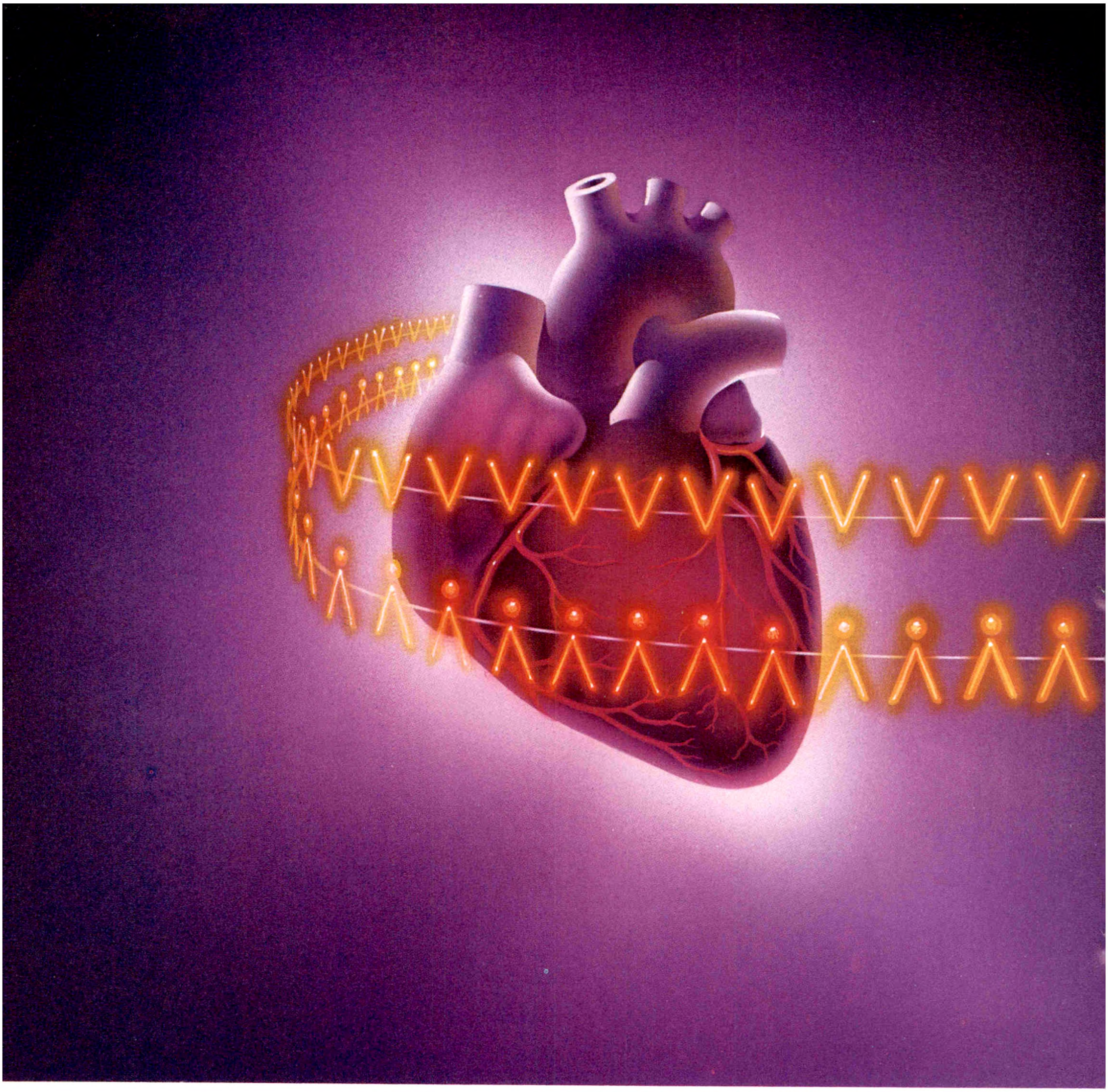

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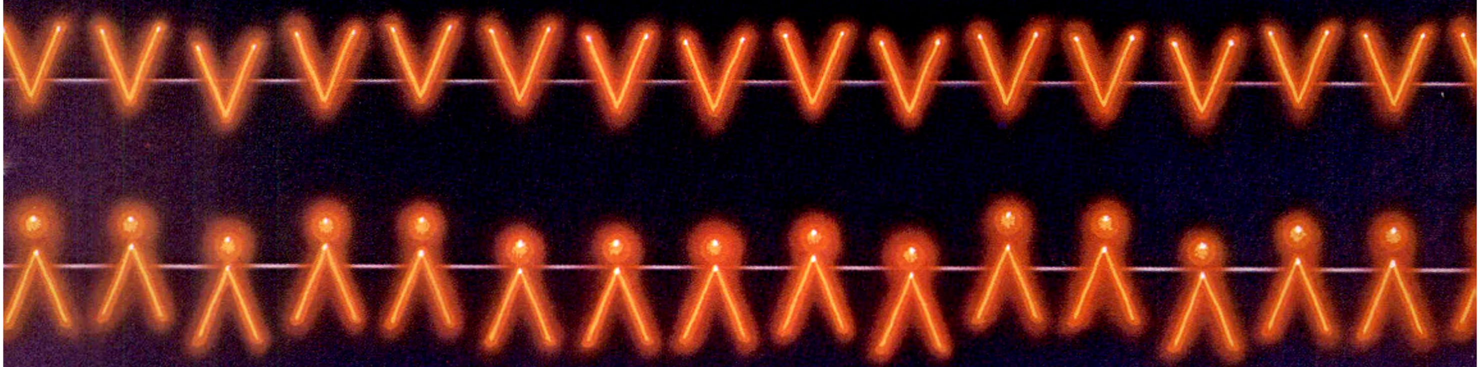

PROVIDES smooth induction[1]

BLUNTS hemodynamic response to intubation and surgical stimulation[2]

REDUCES need for vasoactive drugs in the intraoperative and postoperative periods[1]

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Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%),

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

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OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

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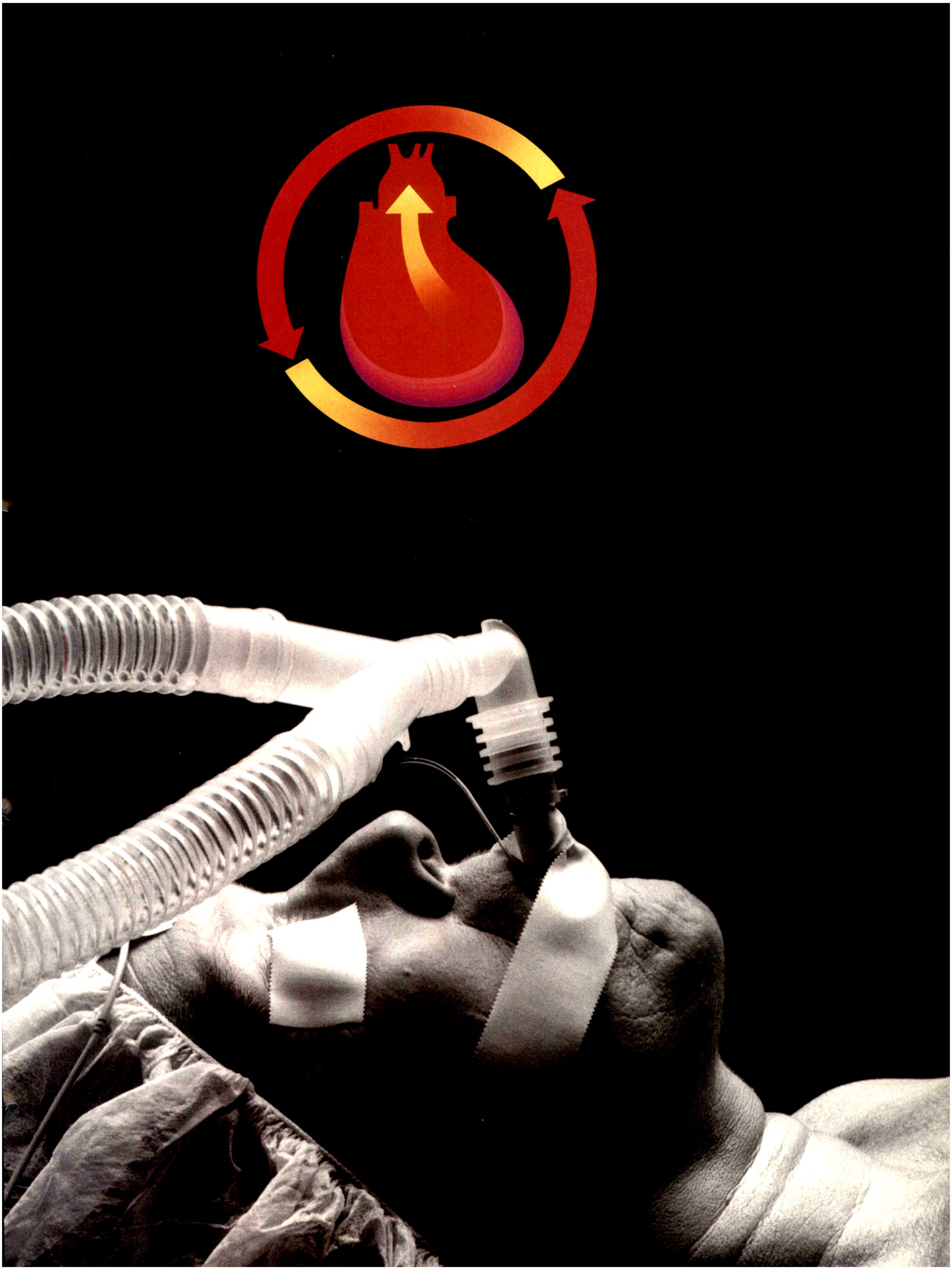

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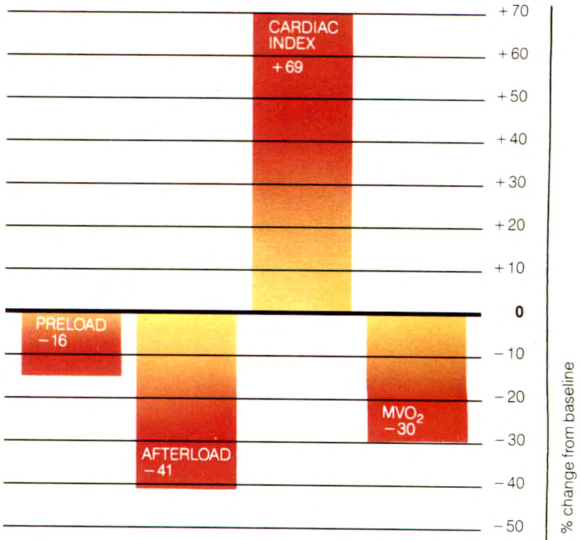

†n = 8. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.[1]

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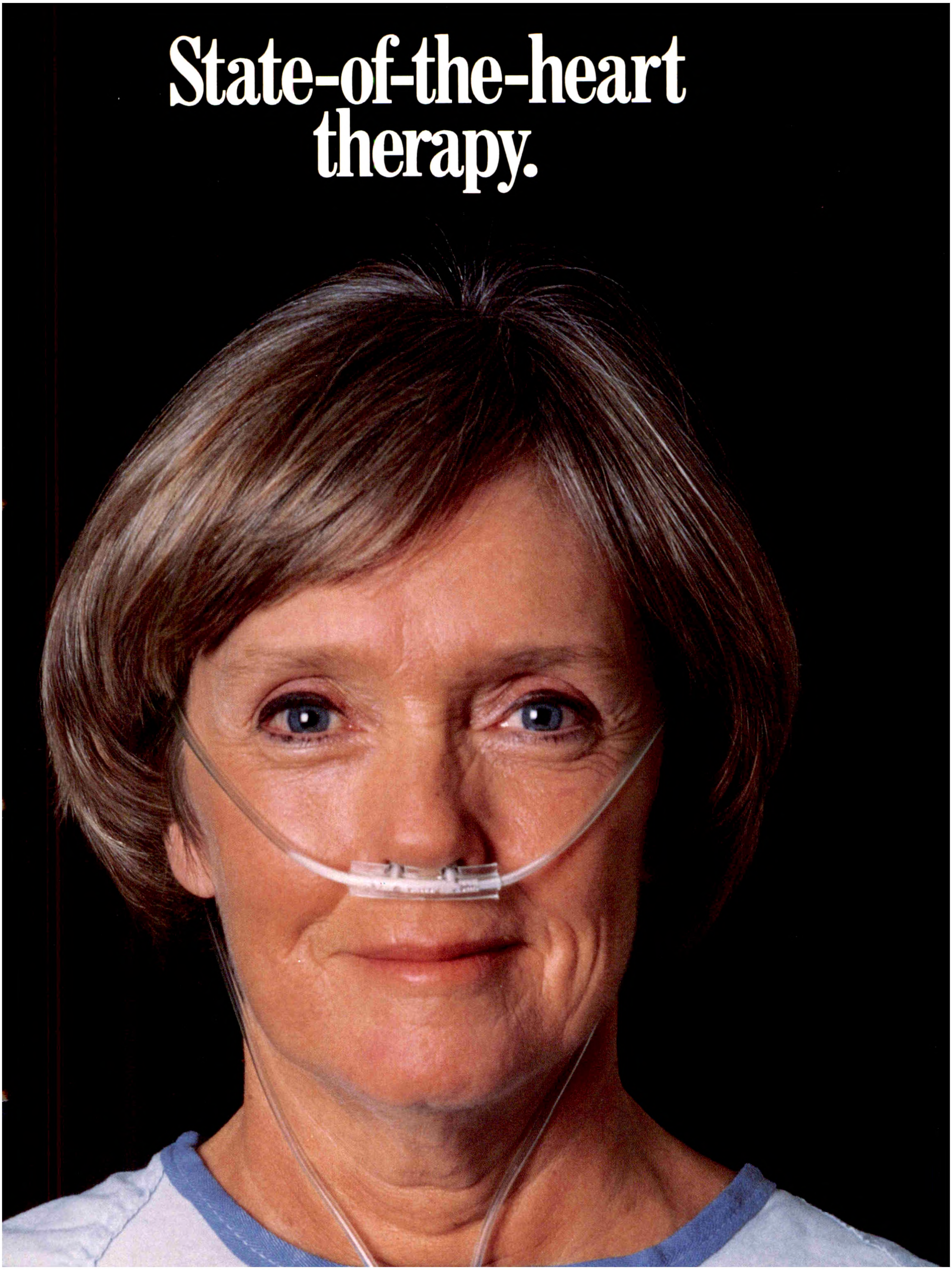
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CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General*: INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C.* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is no certain, but possible hypersensitivity reactions should be considered in an patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinon clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site o injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotensio because of its vasodilator effect. If this occurs, amrinone administration shoul be reduced or discontinued. No specific antidote is known, but genera measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reduction*: Asymptomatic platelet count reduction (to less than 150,000/mm³) may b reversed within one week of a decrease in drug dosage. Further, with no chang in drug dosage, the count may stabilize at lower than predrug levels without an clinical sequelae. Predrug platelet counts and frequent platelet counts durin therapy are recommended to assist in decisions regarding dosag modifications.

Should a platelet count less than 150,000/mm³ occur, the followin actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have eithe stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceed the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were see infrequently with IV therapy, should severe or debilitating ones occur, th physician may wish to reduce dosage or discontinue the drug based on th usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepat toxicity has rarely been observed. If acute marked alterations in liver enzyme occur together with clinical symptoms, suggesting an idiosyncratic hypersens tivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptom these nonspecific changes should be evaluated on an individual basis. Th clinician may wish to continue amrinone and reduce the dosage or discontinu the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containin INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCO lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water fo injection.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

State-of-the-heart

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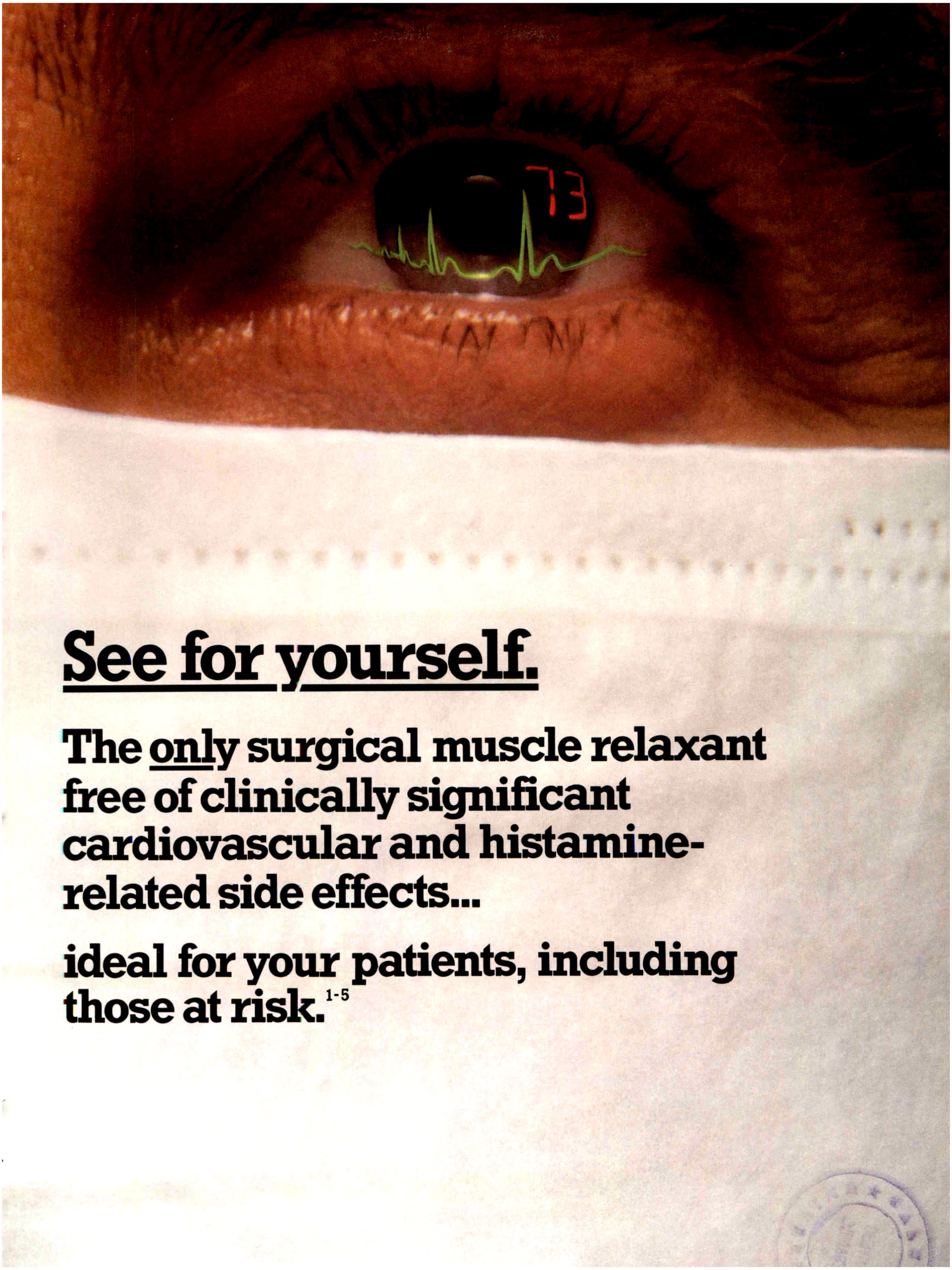
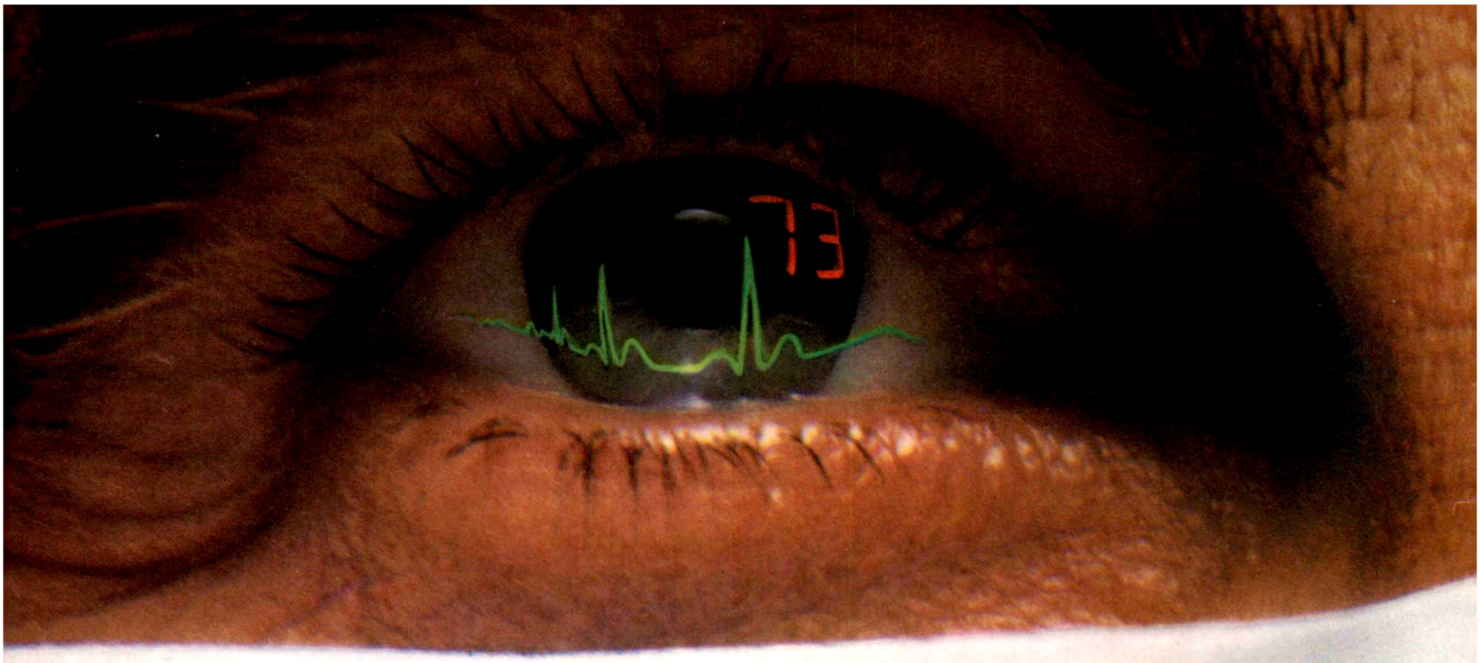


See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

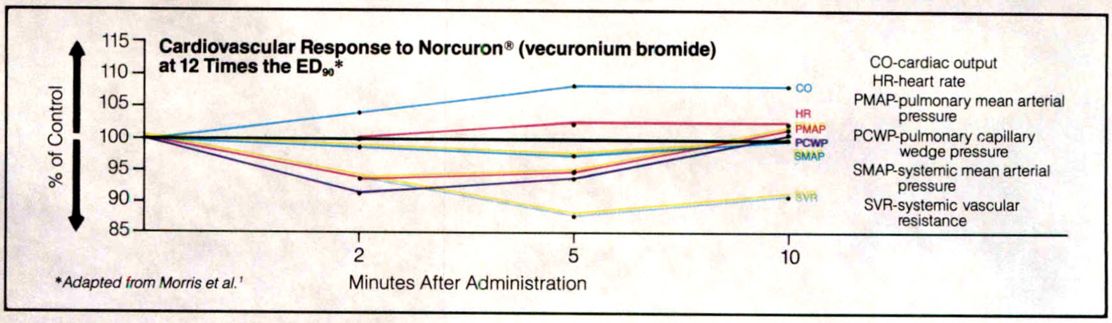
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



Cardiovascular Response to Norcuron® (vecuronium bromide) at 12 Times the ED_{90}*

*Adapted from Morris et al.[1]

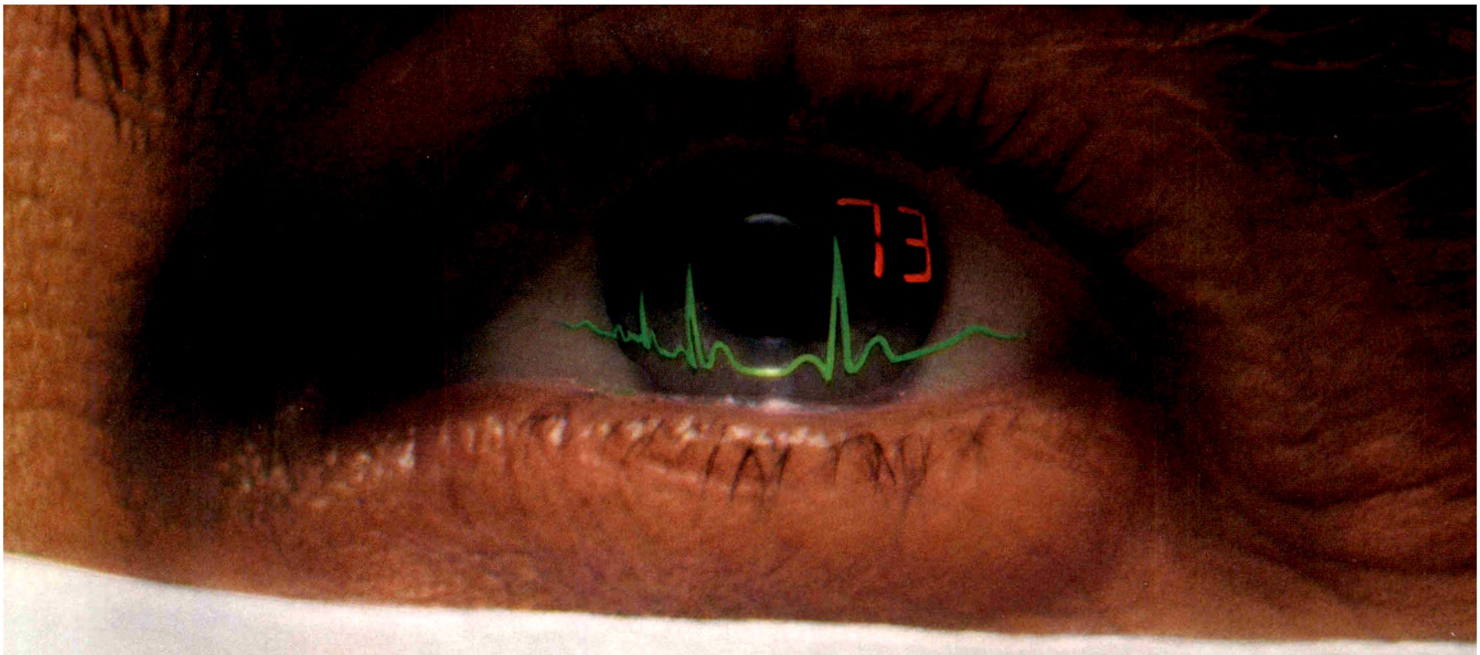
Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

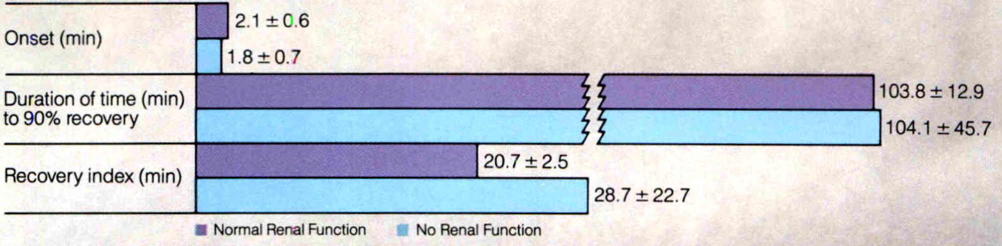
*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.
†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

NO REFRIGERATION REQUIRED

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

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Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

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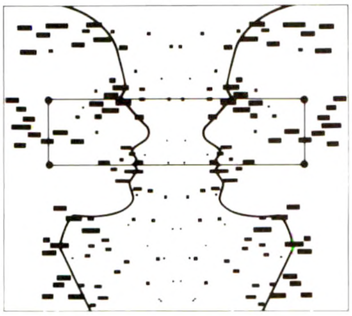

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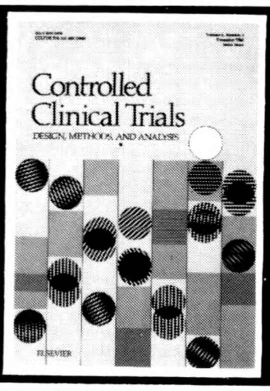

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CONTENTS: List of Contributors. Preface. 1. The pathology of head injury *(D. I. Graham)*. 2. The pathophysiology of head injury *(J. D. Miller)*. 3. Pulmonary function in the head-injured patient *(S. Jennett)*. 4. The clinical assessment of the head-injured patient *(G. Teasdale)*. 5. The immediate care and transportation of the head-injured patient *(S. Galbraith)*. 6. Anaesthesia and the head-injured patient *(J. Barker)*. 7. The post-operative care of the head-injured patient *(J. M. Horton)*. 8. Artificial ventilation in the management of the head-injured patient *(D. G. McDowall)*. 9. Intracranial pressure monitoring in the management of the head-injured patient *(S. Galbraith)*. 10. Extracranial injuries-facial injuries *(J. P. Vance)*. 11. Extracranial injuries-chest injuries *(A. B. M. Telfer)*. 12. The use of barbiturate therapy in the management of the head-injured patient *(H. M. Shapiro, B. J. Dunlop and L. F. Marshall)*. 13. Brain death *(W. Fitch)*. 14. Future developments in the care of the head-injured patient *(B. Jennett)*. Subject index.

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Proceedings of the 2nd International Resuscitation Days
Rome, 2 October 1985

edited by **A. Gasparetto**

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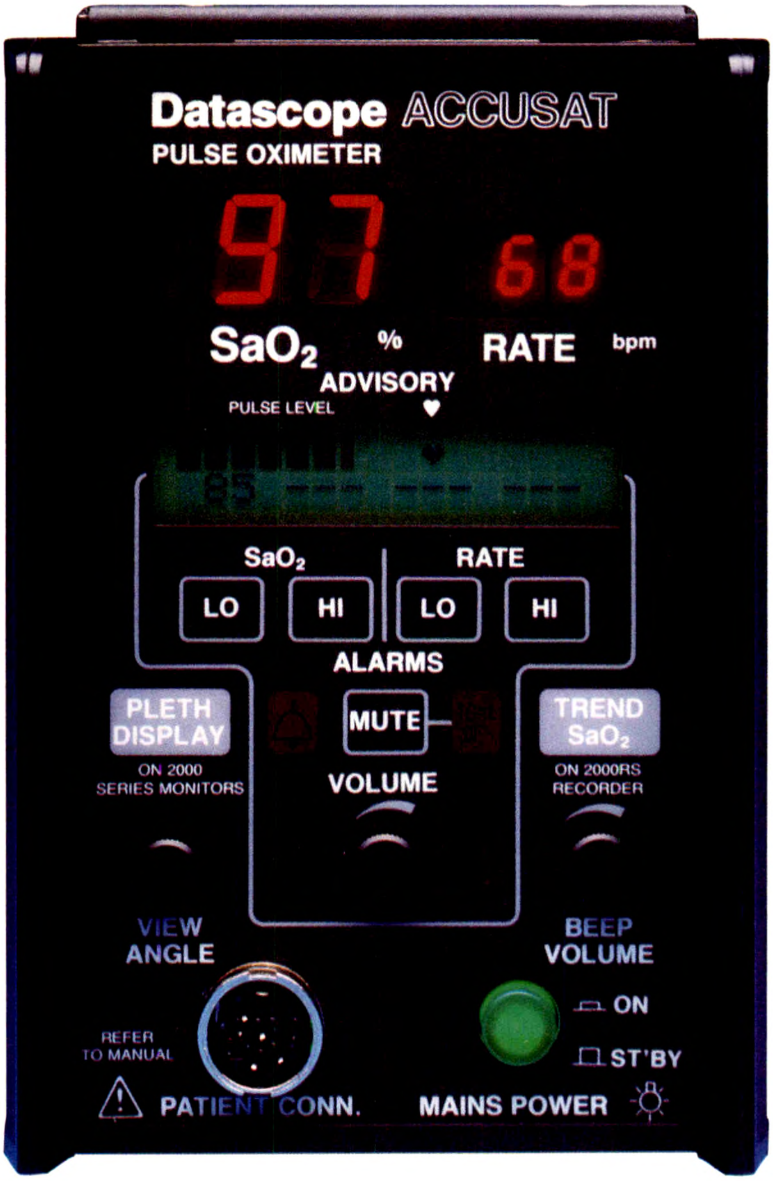

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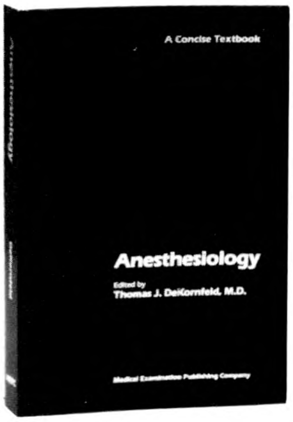

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Pharmacokinetics of Unchanged Morphine in Normal and Cirrhotic Subjects

Jean-Xavier Mazoit, MD, Pierre Sandouk, PhD, Paul Zetlaoui, MD, and
Jean-Michel Scherrmann, PhD

MAZOIT J-X, SANDOUK P, ZETLAOUI P, SCHERRMANN J-M. Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. Anesth Analg 1987;66:293–8.

Published reports of morphine pharmacokinetics differ, perhaps because of analytical discrepancies and different study protocols. A highly specific radioimmunoassay (N-carboxymethylnormorphine RIA) was used to measure unchanged morphine in plasma in six normal subjects and in eight cirrhotic patients with hypoalbuminemia, hyperbilirubinemia, and prolonged prothrombin time. All subjects received a single intravenous bolus of morphine hydrochloride (0.1 mg/kg). Peripheral blood samples were collected at frequent intervals from 2 min to 36 hr after injection. In cirrhotic patients as compared with normal subjects, terminal half-life of unchanged morphine was longer (201 ± 39 vs 111 ± 32 min (mean ± SD), $P < 0.01$) and total body clearance was slower (21 ± 7.5 vs 33.5 ± 8 $ml{\cdot}min^{-1}{\cdot}kg^{-1}$, $P < 0.05$). The apparent volume of distribution and the steady-state volume of distribution did not differ in the two groups. In conclusion, cirrhotic patients have a prolonged terminal half-life of unchanged morphine that is attributable to a decrease in total body clearance.

Key Words: ANALGESICS—morphine. LIVER—cirrhosis. PHARMACOKINETICS—morphine.

Morphine has been said to have a longer terminal half-life in cirrhotic patients than in normal subjects (1). Cirrhosis of the liver usually decreases the rate of elimination of drugs actively metabolized by the liver (2). Removal of a drug from the body is, however, determined by two factors: the apparent volume of distribution and the total body clearance (3). The observed decrease in morphine protein binding due to hypoalbuminemia and hyperbilirubinemia in cirrhotics (1) is expected to have little effect on distribution because the extent of binding is so relatively moderate. Two factors may, however, decrease the clearance of drugs in cirrhotic patients: 1) a decrease in hepatic blood flow or 2) a decrease in hepatic extraction ratio. Again, a decrease in protein binding would have little effect on hepatic clearance of morphine because of the high extraction ratio (4).

On the other hand, the decrease in hepatic blood flow in cirrhosis (5) may have the potential for decreasing morphine clearance. Surprisingly, Patwardhan et al. (6) did not find any difference in morphine kinetics between normal and cirrhotic subjects. We, therefore, used a highly specific radioimmunoassay (RIA) to measure morphine kinetics in normal subjects and in cirrhotics with marked decrease in hepatic function.

Patients and Methods

Patients

Institutional approval was obtained and informed consent was given by 14 subjects, including both sexes. All of them had a normal renal function with normal serum creatinine. Except for a history of alcoholism in the cirrhotic patients, none of the subjects studied were receiving drug therapy, and none had been anesthetized within the previous 3 months. One group consisted of six noncirrhotic volunteers (four males and two females) aged 56 ± 9 yr (mean ± SD) and weighing 68 ± 19 kg. A second group consisted of eight alcoholic cirrhotic patients (six males and two females) aged 64 ± 6 yr and weighing 71 ± 14 kg. Cirrhosis was histologically proved in all but one of the latter patients. Biological criteria to ensure homogeneity in the cirrhotic group included prothrombin times rang-

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ing between 45 and 70% of normal, serum albumin levels less than 3.2 g/dl, and serum bilirubin levels higher than 1.5 mg/dl. None of the patients had had surgical portocaval shunts and none had clinical evidence of ascites.

Sampling and Analysis

All subjects received a single intravenous bolus of morphine hydrochloride (0.1 mg/kg = 0.076 mg/kg morphine base). Peripheral venous blood samples (5 ml) were collected in heparinized tubes 2, 5, 10, 15, 30, and 60 min and 2, 3, 5, 7, 9, 12, 18, 24, and 36 hr after injection. An additional sample was taken at 8 hr in five normal subjects and six cirrhotic patients. Plasma was separated and stored at −20°C until the time of analysis. The unchanged morphine concentrations in plasma were measured by a specific RIA. Morphine antisera were raised in goats by immunization with N-carboxymethylnormorphine (N-CMN) conjugated to bovine serum albumin as described by Gintzler et al. (7). The carrier protein was conjugated to the nitrogen atom of the opiate alkaloid in order to recognize the phenolic hydroxy group on C3 and the alcoholic group on C6. Ammonium sulfate was used to precipitate the morphine antibody complex. The sensitivity, intra- and interassay reproducibilities, and linearity of the RIA for morphine were determined: 16 pg of morphine could be reliably assayed, with ^{3}H-morphine (60 Ci/mmol) (New England Nuclear, Boston, Mass.) as labeled antigen. The coefficient of variation for reproducibilities varied from 7.7 to 12.0% at concentrations ranging from 0.1 to 60 ng/ml.

The specificity of the RIA was studied by measuring the percentage of cross-reactivity of various morphine congeners that inhibit labeled hapten antibody complex at 50%. The cross-reactivities of morphine 3-0-glucuronide, the major morphine metabolite, and of codeine were below 0.2%. 6-Monoacetylmorphine, an analogue of 6-0-glucuronide, had 0.5% cross-reactivity. Normorphine, a minor metabolite of morphine, had 30% cross-reactivity (but it would not be expected to interfere because its concentration would be quite low after a single dose of morphine). Naloxone, the major morphine antagonist, had a lower cross-reactivity (1%). The cross-reactivity was also studied in triplicate by adding to opiate-free plasma cross-reacting compounds at two different concentrations (Table 1). A linear least-squares regression program for logit-log transformation was used for linearization of the standard curve and calculation of the amount of morphine in patient samples. Morphine is expressed in terms of equivalents of morphine base.

Table 1. Morphine Equivalents of Several Compounds Determined by Radioimmunoassay (n = 3) (Morphine Recovery = 95–102%)

	Added drug (ng/ml)	Morphine equivalents measured (ng/ml) (mean ± SD)
Morphine	10	9.8 ± 0.3
	40	40.3 ± 0.5
Morphine 3-glucuronide	50	0
	100	0
Codeine	10	0
	40	0
Normorphine	10	0.9 ± 0.5
	40	11 ± 0.5
6-Monoacetylmorphine	10	0
	40	0

The blood/plasma concentration ratio was measured in vitro. Then, 52.6 ng and 13.2 ng of morphine hydrochloride (corresponding to 40 and 10 ng of morphine base, respectively) were added in aliquots (1 ml) of fresh heparinized blood collected in six normal volunteers similar in age and weight to the previous normal subjects studied. After 45 min at 37°C, morphine was measured both in blood and plasma.

Pharmacokinetic Analysis and Statistics

Individual serum concentration data were fitted according to a two-compartment open model as follows:

$$C = C_1 e - \lambda_1 t + Cz e - \lambda zt$$

using a nonlinear least-squares regression program (PCNONLIN) (8). The data were weighted by the reciprocal of the concentration squared. The area under the curve (AUC), the terminal half-life ($t_{1/2}$), the distribution half-life ($t_{1/2\lambda 1}$), the volume of the central compartment (V_c), the volume of distribution (V_z), the volume of distribution at steady state (V_{ss}), and the total body clearance (CL) were calculated as follows:

$$\mathrm{AUC} = C_1/\lambda_1 + C_z/\lambda_z$$

$$t_{1/2} = 0.693/\lambda_z$$

$$t_{1/2}\lambda_1 = 0.693/\lambda_1$$

$$V_c = \mathrm{Dose}/(C_1 + C_z)$$

$$V_z = \mathrm{Dose}/(\mathrm{AUC}\cdot\lambda_z)$$

$$V_{ss} = \mathrm{Dose}(C_1/\lambda^2{}_1 + C_z/\lambda^2{}_z)/\mathrm{AUC}^2$$

$$\mathrm{CL} = \mathrm{Dose}/\mathrm{AUC}$$

Data are expressed as the mean ± standard deviation. Statistical analysis was performed using the

Table 2. In Vitro Blood/Plasma Concentration Ratio

	Subjects (Hematocrit: 41 ± 2%)						
Concentration	1	2	3	4	5	6	Mean ± SD
40 ng/ml	1.12	1.24	1.18	1.26	1.33	1.22	1.22 ± 0.07
10 ng/ml	1.14	1.15	1.29	1.16	1.37	1.11	1.20 ± 0.07
							1.21 ± 0.08

Table 3. Major Biochemical Data (Mean ± SD)

Subjects	Age (yr)	Weight (kg)	Alkaline phosphatase (mU/ml)	Serum albumin (g/dl)	Prothrombin time[a] (% N)	Serum bilirubin (mg/dl)	Serum creatinine (mg/dl)	Hemoglobin (g/l)
Normals								
1 F	54	46	—	4.4	100	0.3	0.9	12.3
2 M	41	87	—	4.3	100	0.3	1.2	14
3 F	69	54	—	4.0	100	0.4	0.9	13.3
4 M	54	56	—	3.9	100	0.3	1.1	13.4
5 M	59	78	—	4.3	100	0.6	0.9	12.7
6 M	61	89	—	4.2	100	0.3	1.0	14.6
Mean	56	68	—	4.2	100	0.35	1.0	13.4
SD	9	19	—	0.2		0.1	0.1	0.8
Cirrhotics								
1 M	71	55	106	2.3	45	1.6	0.9	13.6
2 M	61	77	84	3.1	50	3.5	0.7	12.5
3 M	54	48	96	3.1	45	5.6	1.0	14.1
4 M	68	85	108	2.5	45	2.4	0.8	13.2
5 M	70	66	45	3.1	60	1.6	0.8	12.8
6 M	59	88	75	3.0	45	2.0	1.1	11.9
7 F	69	79	58	3.0	65	2.7	0.7	11.6
8 F	60	68	63	2.3	70	1.6	0.8	12.6
Mean	64	71	79	2.8	50	2.6	0.85	12.8
SD	6	14	23	0.4	10	1.4	0.1	0.8
	NS	NS		$P < 0.01$		$P < 0.01$	NS	NS

[a] Expressed in percent of normal

nonparametric Mann-Whitney *U*-test. A level of $P < 0.05$ was considered the minimum level of significance.

Results

The blood/plasma concentration ratio did not differ at the two concentrations assayed (1.21 ± 0.08) (Table 2). Cirrhotic patients had significantly different prothrombin times, serum albumin, and serum bilirubin levels when compared with normal subjects (Table 3).

Unchanged Morphine Kinetics (Table 4 and Fig. 1)

No morphine was detected in plasma after the seventh hour in normal subjects (except in patient 3) and after the 12th hour in all cirrhotic patients. Terminal half-life ($t_{1/2}$) was longer, total body clearance (CL) was significantly slower, and AUC was significantly increased in cirrhotic patients as compared with noncirrhotic subjects. The steady-state volume of distribution (V_{ss}) and the apparent volume of distribution (V_Z) did not differ significantly between the two groups.

Discussion

Normal Subjects

A summary of data from several recent pharmacokinetic studies of morphine is shown in Table 5 (4,6,9–11). Differences in patient sampling and analytical methods may account for the variations in these data. Analysis based on 3-0-carboxymethylmorphine RIA is extremely sensitive, but suffers from a potential lack of specificity (12). Specific RIA methods have been reported (7,13). The most specific of these is obtained when the antiserum is raised against N-carboxy-methylnormophine: the relationship between antiserum specificity and immunogen structure is based

Table 4. Pharmacokinetic Parameters of Unchanged Morphine (Mean ± SD)

Subjects	AUC ($ng \cdot min^{-1} \cdot ml^{-1}$)	C_1	C_z	$t_{1/2\lambda 1}$ (min)	$t_{1/2}$ (min)	V_c (L/kg)	V_z (L/kg)	V_{ss} (L/kg)	CL ($ml \cdot min^{-1} \cdot kg^{-1}$)
Normal									
1	1718	70.8	13.4	3.3	72	0.91	4.57	3.77	44
2	1964	55.7	8.6	6.8	111	1.18	6.25	4.46	39
3	2715	72.3	9.4	5.4	156	0.93	6.30	4.96	28
4	2007	50.1	9.5	4.9	121	1.27	6.63	5.51	38
5	2231	41.3	17.2	4.6	79	1.30	3.88	3.44	34
6	4270	141	21.3	1.4	129	0.47	3.35	3.09	18
Mean	2484	71.9	13.2	4.4	111	1.01	5.16	4.21	33.5
SD	937	35.9	5.1	1.9	32	0.31	1.41	0.93	9
Cirrhotics									
1	6796	40.5	15.1	13.0	277	1.37	4.48	4.03	11
2	2556	16.0	3.9	15.5	199	3.21	8.53	3.84	30
3	2304	61.9	6.3	7.7	179	1.11	8.52	6.16	33
4	4712	32.4	15.2	7.9	198	1.60	4.60	4.28	16
5	3773	38.6	15.1	11.8	143	1.41	4.15	3.50	20
6	3836	35.1	13.3	7.5	180	1.57	5.14	4.66	20
7	5084	35.8	15.8	9.1	202	1.47	4.34	3.99	15
8	3166	40.2	6.1	20.1	229	1.64	7.00	5.34	24
Mean	4028	37.6	11.4	11.6	201	1.67	5.84	4.48	21
SD	1475	12.6	5.0	4.5	39	0.64	1.88	0.88	7.5
	$P < 0.05$	$P < 0.01$	NS	$P < 0.01$	$P < 0.01$	$P < 0.01$	NS	NS	$P < 0.05$

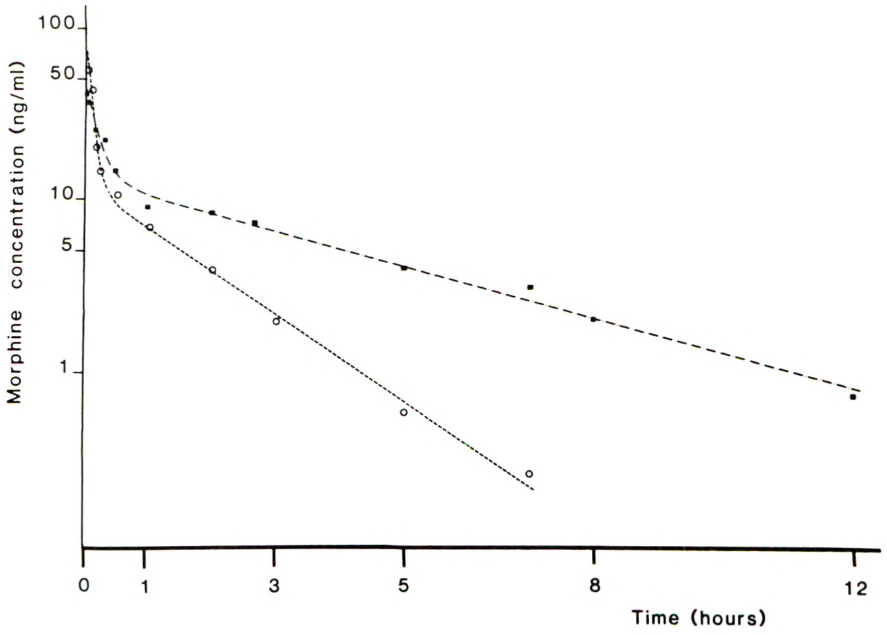

Figure 1. Concentrations of unchanged morphine in plasma vs time for a normal volunteer and a cirrhotic patient.

○------- Normal subject (no. 1)
■—·—·— Cirrhotic patient (no. 6)

on the position of attachment of the hapten to the carrier protein (7,13,14). The specificity of our antiserum is very high, as shown by the study of cross-reactivity and the recovery of morphine and metabolites. We, therefore, used an intravenous dose (0.1 mg/kg morphine hydrochloride) corresponding to the usual therapeutic dose. The initial decline of unchanged morphine concentration in plasma was rapid. The $t_{1/2}$ and CL were shorter and faster, respectively, than in most previous studies, but are in good agreement with the recent study of Säwe et al. (11), whose measurements were made with ion-paired HPLC. However, differences in patient populations between the cited studies may be more important than assay differences.

Morphine, which has a moderate extent of plasma protein binding (1,6) but a high hepatic extraction ratio (4), is assumed to be nonrestrictively cleared by

Table 5. Major Morphine Pharmacokinetic Parameters in the Literature (Noncirrhotic Subjects)

Authors	Patients	Analytical method	$t_{1/2}$ (min)	V_z (L/kg)	V_{ss}	CL ($ml \cdot min^{-1} \cdot kg^{-1}$)
Stanski et al., 1978 (4)	Young, healthy, awake	3-OCMM RIA	177	3.2	—	14.7
Sāwe et al., 1981 (9)	Cancer patients, awake	GLC	187	2.08	—	9.2
Patwardhan et al., 1981 (6)	Middle aged, awake	GLC	150	3.7	—	16.2
Murphy et al., 1981 (10)	Young, ASA I–II, anesthetized	Solvent extraction 3-OCMM RIA	104	3.4	—	23
Sawe et al., 1985 (11)	Cancer patients, awake	HPLC	102	4.0	—	28.0
Present study, 1986	Sixth–seventh decade, awake	N-CMN RIA	111	5.2	4.2	33.5

Abbreviations: 3-OCMM RIA, 3-0-carboxymethylmorphine radioimmunoassay; GLC, gas liquid chromatography; HPLC, ion-pair high-performance liquid chromatography; N-CMN RIA, N-carboxymethylnormorphine radioimmunoassay.

the liver (2,4). In other words, elimination of morphine by the liver depends mainly on hepatic blood flow. In the "tug-of-war" model (15), "flow-limited" drugs are expected to have a greater affinity for hepatic enzymes than for plasma proteins and red blood cells. Thus, with a blood plasma concentration ratio of 1.1 [Patwardhan (6)] to 1.21 (present study), the total blood clearance would not be expected to be lower than 25 $ml \cdot min^{-1} \cdot kg^{-1}$. Assuming a hepatic extraction ratio (E) of 0.70 (4) and a hepatic blood flow (HBF) of 25 $ml \cdot min^{-1} \cdot kg^{-1}$ (16), hepatic clearance calculated as E × HBF would not be expected to exceed 17.5 $ml \cdot min^{-1} \cdot kg^{-1}$. But in addition to a 10% renal excretion of morphine (17), extrahepatic biotransformation of morphine cannot be excluded.

Extrahepatic conjugation of morphine with glucuronic acid has been demonstrated in some species (18) and suspected in humans (6). Further studies are needed to confirm or invalidate this hypothesis.

Cirrhotic Patients

In the present study, elimination of unchanged morphine was prolonged in alcoholic cirrhotic patients, the terminal half-life being twofold greater than in normal subjects. In 1975, Olsen et al. (1) showed that plasma protein binding of morphine was decreased in a group of patients with hepatic failure. This decreased binding was attributed to lower serum albumin levels plus displacement of the bound drug due to the high binding affinity of bilirubin. Nevertheless, this higher free fraction of drug in plasma would not be expected to increase the volume of distribution because of the normally only moderate extent of protein binding (1,6).

In our study, neither V_{ss} nor V_z differed significantly between the two groups, and this is consistent with the above statement. The lower CL in the cirrhotic group is in accordance with the assumption that elimination of morphine by the liver depends mainly on hepatic blood flow (2,4). Cirrhosis of the liver usually decreases hepatic blood flow (5). We did not measure hepatic blood flow by, e.g., ICG clearance in our subjects. However, Patwardhan et al. had only two cirrhotics with marked decrease in ICG clearance, which may explain their failure to demonstrate altered kinetics in cirrhotics (6). Another factor that may decrease hepatic clearance of morphine in cirrhosis is a decrease in hepatic extraction ratio. The cirrhotics studied by Patwardhan et al. seemed to be in moderate hepatic failure. They had hypoalbuminemia and hyperbilirubinemia and three had ascites. Nevertheless, all had normal prothrombin times. The subjects we studied seemed to have a more significant hepatic disturbance. All had prolonged prothrombin times and were icteric. So, a decrease in the hepatic extraction ratio may have had an additional effect on the decreased hepatic clearance in our patients when compared with those of Patwardhan et al.

In conclusion, the pharmacokinetics of morphine are altered in cirrhotic patients without ascites who have impaired hepatic function. The increase in terminal half-life is due to a lower total body clearance without a significant change in the volume of distribution. Either a decrease in hepatic extraction ratio or a decrease in hepatic blood flow (or both) may have caused the decrease in morphine clearance in cirrhotics. Our study does not allow identification of which of these two mechanisms is responsible for the observed decrease in clearance. In clinical practice, therefore, in cirrhotic patients the dosing interval with morphine should be increased about 1.5-fold to twofold in order to avoid accumulation and deleterious effects.

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A Randomized Prospective Controlled Study of the Metabolism and Hepatotoxicity of Halothane in Humans

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COUSINS MJ, GOURLAY GK, KNIGHTS KM, HALL P DE LA M, LUNAM CA, O'BRIEN P. A randomized prospective controlled study of the metabolism and hepatotoxicity of halothane in humans. Anesth Analg 1987; 66:299–308.

In a randomized prospective controlled study in humans, the metabolism and hepatic effects of a single administration of halothane were compared with enflurane and meperidine. Pre- and postoperative antipyrine pharmacokinetics, intraoperative indocyanine green clearance, liver histology, and postoperative liver function tests were determined in 24 patients undergoing abdominal surgery who were randomly allocated to receive either halothane (0.5%, group I), enflurane (0.8%, group II), or meperidine (group III) as a supplement to a common basal anesthetic regimen consisting of thiopental, nitrous oxide/oxygen/muscle relaxant. In addition, end-tidal concentrations of the volatile reductive metabolites of halothane, chlorodifluoroethylene (CDF), and chlorotrifluoroethane (CTF) were determined in group I patients and serum and urinary inorganic fluoride were determined in both group I and II patients. Indocyanine green clearance was measured before anesthesia (stage I), during basal anesthesia (stage II), in the presence of surgical stimuli (stage III), and after introduction of the selected anesthetic agent (stage IV). CDF and CTF were detectable within 20 min of the start of halothane anesthesia in every patient receiving halothane. Peak serum fluoride concentrations occurred at 2 and 24 hr in the enflurane and halothane groups, respectively, whereas urinary fluoride excretion was elevated postanesthesia in the enflurane group only. There was no difference between the pre- and postoperative disposition of antipyrine in group II or III, but after anesthesia, antipyrine clearance was significantly decreased ($P < 0.02$) and plasma half-life increased ($P < 0.05$) in group I patients (halothane). Concentrations of serum alanine aminotransferase (ALT) and bilirubin were significantly elevated ($P < 0.05$) postoperatively in groups I and II but unchanged from preoperative values in group III patients. Three of the 24 liver biopsies taken at the end of stage IV showed several foci of acute liver cell necrosis; of these, two patients were from group I and one from group II. There were no significant differences in liver cell morphology ($P > 0.5$) in biopsies taken at the end of stage IV compared with biopsies at the end of stage III, from groups I and II. The results of this study show that reductive metabolism of halothane occurs routinely in patients undergoing halothane anesthesia under conditions of normoxia. This may be the cause of the changes in antipyrine clearance after halothane anesthesia.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane. BIOTRANSFORMATION (DRUG)—halothane. LIVER—hepatitis.

The National Halothane Study was a retrospective study designed to detect cases of massive hepatic necrosis following halothane anesthesia (1); however, its design led to equivocal results. Retrospective assessment of reports to the Committee on Safety of Medicines in the United Kingdom indicated an incidence of jaundice after repeated halothane administration that was greater than that seen after other anesthetics (2). Later this committee reported that the death rate from "halothane hepatitis" was 51–52% after multiple exposures compared with 35% after a single exposure. Subsequently, comparative prospective studies confirmed that the incidence of liver dysfunction after repeated halothane exposure was greater than after other anesthetics (3–5), although other studies were not in agreement (6,7).

Recent clinical studies have demonstrated an incidence (20–40%) of transient abnormalities in liver function after repeated halothane anesthesia (5) but not after a single exposure to either halothane or enflurane (8). Enflurane has been favored as an alter-

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Table 1. Measurement of Indocyanine Green Clearance

Stage I	Stage II	Stage III	Stage IV
	Thiopental		
	N_2O/O_2	N_2O/O_2	N_2O/O_2
	Pancuronium		
	"Basal anesthesia"		"Supplement"
Preanesthesia	Postinduction	During surgery	During surgery
		↑	↑
		Liver biopsy 1	Liver biopsy 2
C_{ICG}	C_{ICG}	C_{ICG}	C_{ICG}

native to halothane, particularly if repeated administrations are necessary. However, reports have appeared in the literature of enflurane-associated hepatotoxicity (9,10); the clinical, biochemical, and histological features have some similarities to those documented for both halothane- and methoxyflurane-induced hepatic injury (11).

Multiple determination of antipyrine pharmacokinetics in individuals has been used extensively to quantitate the effect of an environmental variable such as paracetamol overdosage on the hepatic mixed-function oxidase system (12). In patients with acute liver damage, prolongation in the plasma half-life of antipyrine has been observed (13). It would appear, therefore, that determination of antipyrine pharmacokinetics before and after anesthesia may detect transient abnormalities in hepatocellular function associated with either halothane or enflurane administration.

The present study is the first randomized prospective controlled study in humans of the metabolism and hepatic effects of a single administration of halothane compared with another halogenated agent (enflurane) and an opioid supplement (meperidine) superimposed upon a standardized "basal" anesthetic regimen.

Materials and Methods

Study Design

This study was approved by the Drugs and Therapeutics Advisory Committee and the Clinical Investigation Committee, Flinders Medical Centre. Adult patients, ASA status I–II, admitted for elective abdominal surgery were included in the study after informed consent had been obtained, including permission for liver biopsy. All patients were under the care of the same surgeon and patients with malignant disease or preoperative liver dysfunction were excluded from the study. Patients were randomly assigned to receive halothane (group I, $n = 8$), enflurane (group II, $n = 8$), or meperidine (group III, $n = 8$) as a supplement to a basal anesthetic (see below). Sedation the night before the operation consisted of oral diazepam, 10 mg.

Anesthesia and Monitoring

Atropine, 0.01 mg/kg, and meperidine, 1.33 mg/kg, were given intramuscularly 1 hr prior to expected arrival time in the operating room. A peripheral intravenous cannula was inserted in one arm. A centrally directed venous line with a double three-way stopcock was inserted in the contralateral arm the day prior to surgery for the determination of antipyrine pharmacokinetics (see below). General anesthesia was induced with thiopental, 5 mg/kg, followed by succinylcholine, 1 mg/kg, to facilitate tracheal intubation. Maintenance anesthesia consisted of nitrous oxide/oxygen (70:30) delivered via a semiclosed-circle system, plus supplementation with either halothane (group I) or enflurane (group II) at end-tidal concentrations of 0.5 and 0.8%, respectively, or a meperidine infusion consisting of a loading infusion (60 mg over 10 min) and then a maintenance infusion of 25 mg/hr (group III). Pancuronium bromide, 0.08 mg/kg, was used as a muscle relaxant in all groups.

Ventilation was mechanically controlled to maintain a normal arterial carbon dioxide tension (40 torr) in radial arterial blood. End-tidal halothane and enflurane concentrations were monitored with an infrared analyzer and end-tidal percent carbon dioxide and percent oxygen were adjusted to 5% and 30%, respectively, with the aid of a Centronic MGA 200 mass spectrometer.

Arterial blood pressure was measured and continuously recorded via a 20-gauge radial artery cannula as previously described (14).

Antipyrine Pharmacokinetics

Antipyrine (10 mg/kg) was injected into a peripheral vein in the arm opposite to that used for blood sampling. Blood samples (4 ml) were collected into heparinized tubes at 0, 30, 60, 90, 120 min and thereafter at 2-hr intervals for a total of 24 hr. In all groups, antipyrine clearance was determined 24 hr preoperatively and 48 hr after anesthesia.

Blank blood collected prior to the administration of the antipyrine was used for preparation of the standard curve. Antipyrine was added to 1 ml blood to yield drug concentrations of 5, 10, 20, 30, and 40 μg/ml. Cyproheptadine (4 μg/10 μl) was used as the internal standard in all samples. To blood (1 ml) or standards was added 0.2 ml, 0.1N NaOH and 3 ml ether. The sample was mixed (vortex mixer, 1 min), centrifuged at 3000 rpm for 5 min, and subsequently frozen in methanol plus dry ice. The ether layer was transferred to tubes containing 1N HCl (0.2 ml), vortex mixed, centrifuged, and refrozen. The ether was decanted and the frozen layer heated at 50°C for 10 mins to evaporate residual ether. The remaining solution was transferred to 1-ml Reacti-Vials (Pierce Chemical Company) containing 0.1 ml 5N NaOH. Methylene chloride (50 μl) was injected under the surface and the vials capped, vortex mixed, and centrifuged. The lower phase (1 μl) was analyzed by gas chromatography as previously described (15).

Indocyanine Green Clearance

Indocyanine green (ICG) clearance (C_{ICG}), an indirect index of hepatic blood flow, was measured before anesthesia (stage I), during "basal anesthesia" with nitrous oxide/oxygen and muscle relaxant (stage II), in the presence of surgical stimuli (stage III), and after the introduction of halothane, enflurane, or meperidine (stage IV) (Table 1). Then, ICG (20 mg, 2.0 ml) was injected as a bolus into a peripheral vein. Blood samples (2 ml) were withdrawn from the blood sampling catheter prior to injection of the ICG and at 1-min intervals for 8 min, with a further sample at 10 min. Plasma ICG was quantitated spectrophotometrically at 805 nm (16).

Anesthetic Metabolites

Concentrations of the volatile reductive metabolites chlorodifluoroethylene (CDF) and chlorotrifluoroethane (CTF) of halothane were measured (17) in end-tidal breath samples collected from all patients in group I at 20-min intervals during halothane anesthesia (stage IV). Serum and urinary inorganic fluoride concentrations (18) were determined pre-, intra-, and postoperatively and 24 hr pre- and postoperatively in patients from groups I and II, respectively.

Liver Histology

An initial liver biopsy (by needle) was obtained immediately after the abdomen was opened (stage III) before either halothane, enflurane, or a meperidine infusion was commenced. At the end of the surgical procedure, prior to closure of the abdomen, a second needle biopsy of the liver was obtained (Table 1). The biopsies were fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin and "routine" liver stains. The paired biopsies were examined by a pathologist (P.H.) who was unaware of the anesthetic regimens. Subsequently, the pairs of liver biopsies from four patients in the halothane and enflurane groups were selected, at random, for quantitation. The image of sections stained by periodic acid-Shiff after diastase digestion was projected to a flat surface using a Lietz Dialux projecting microscope with a final projected magnification of ×830. Mononucleate hepatocytes with clearly distinguishable cell outlines were traced on drawing paper. Two central vein and two portal tract areas were randomly selected from each biopsy; morphologic features of 30 hepatocytes from each area were quantitated.

Individual cell and nuclear areas were measured from each trace using a Houston Instruments Hipad digitizer interfaced to a Northstar Advantage computer. Hepatocyte areas in central vein regions from biopsies taken at the end of the anesthetic "supplement" (stage IV) were compared with hepatocyte areas before anesthesia with either halothane or enflurane using a two-way analysis of variance with repeated measurements on one factor. Hepatocyte areas were similarly compared between portal tract and central vein regions. Nuclear areas, both within and between groups, were analyzed as above and a level of significance of $P < 0.05$ was used to reject the null hypothesis. Mean hepatocyte and nuclear volume were calculated using Loud's formula (19).

Biochemical Assays

Twenty-four hours prior to surgery and for 2 days postoperatively, blood was collected for measurement of electrolyte (Na^+, K^+, Cl^-, HCO_3^-) and glucose levels and liver function tests, including total protein, albumin, bilirubin, creatinine, alkaline phosphatase,

Table 2. Patient Data

	Halothane	Enflurane	Meperidine
Age (yr)	53 ± 15.4	47.8 ± 19.7	55 ± 3.6
Weight (kg)	92.9 ± 27.4	78.3 ± 28.5	76.1 ± 30.2
Sex (M/F)	5/3	3/5	5/3
Duration of volatile anesthesia (min)	93.5 ± 47.2	93.1 ± 17.5	—[a]

Data are expressed as mean ± SD.
[a] Mean length of surgery in this group was 90 min.

alanine aminotransferase (ALT), lactate dehydrogenase, and gamma glutamyl transpeptidase. Assays were undertaken using SMA 6/60, SMA plus, Beckman TR enzyme activity and glucose autoanalyzers.

Pharmacokinetic and Statistical Analysis

The pharmacokinetic parameters of antipyrine disposition were calculated with the aid of a digital computer from the coefficients and exponents of the polyexponential equation describing the blood antipyrine–time curves according to the methods of Wagner (20).

Pre- and postanesthetic data for each variable from all groups were compared using paired Student's *t*-test and an analysis of variance was used to determine the statistical significance of differences within and between groups for C_{ICG} with respect to stages I–IV. To reject the null hypothesis, a level of significance of at least $P < 0.05$ was used. Logarithmic transformations of the data were undertaken, if necessary, to "correct" the inequality of variances (21).

Results

Patient Data

General patient characteristics were similar for all groups studied, with a mean age and weight of approximately 50 yr and 85 kg, respectively; the male-to-female ratio of 5:3 was identical in group I (halothane) and group III (meperidine). The enflurane patients (group II) consisted of three males and five females. In group I, three female patients were obese, 118.5 ± 19.7 kg; there were two obese female patients in groups II and III, 122.7 ± 7.2 and 117.2 ± 7.2 kg, respectively (mean ± SD). The mean time of supplementation with either halothane, enflurane, or meperidine was approximately 90 min in each group (Table 2). Blood gas analysis of samples obtained from the radial artery during stage III were similar for all groups studied, P_{O_2} 115.6 ± 13.3 torr, P_{CO_2} 39.8 ± 3.9 torr, and pH 7.37 ± 0.03 (mean ± SD).

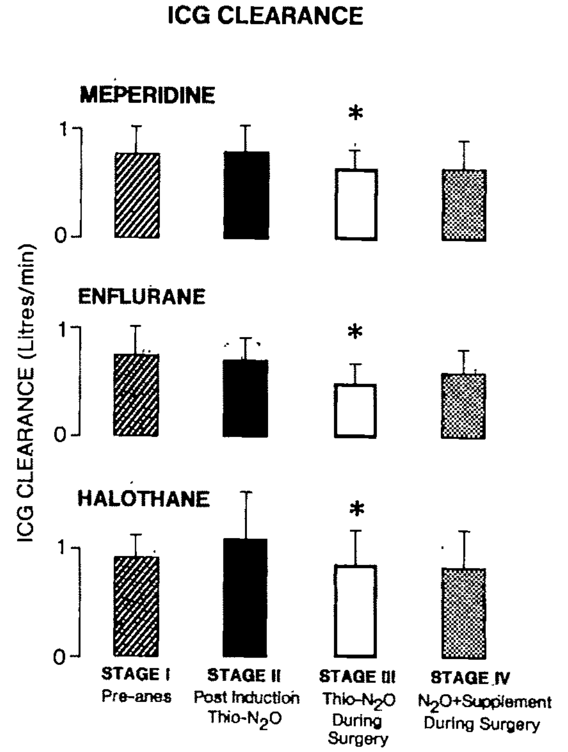

Figure 1. ICG clearance was determined in all patients studied. Clearance is expressed as L/minute and the data are presented as mean ± SD for eight patients in each group. Statistical significance of stage III vs stage I, $P < 0.05$*.

Indocyanine Green Clearance (C_{ICG})

At stage III (i.e., in the presence of basal anesthesia and surgical stimuli), C_{ICG} was significantly ($P < 0.05$) decreased (30–50%) below preanesthetic clearance (stage I) in all groups (Fig. 1). The C_{ICG} determined after induction of anesthesia (stage II) was similar to the preanesthetic values (stage I). Similarly, C_{ICG} with the supplementary agent (stage IV) in the presence of surgical stimuli was not dissimilar from the preanesthetic values in the three groups studied.

Radial Artery Blood Pressure Measurement

Mean (± SD) arterial blood pressure at stage II (basal anesthesia) was not significantly different in group I (87.3 ± 10.2 mm Hg), group II (85.8 ± 11.1 mm Hg), and group III (82.07 ± 10.5 mm Hg) patients. When comparing stage II and stage IV, the introduction of halothane, enflurane, or meperidine did not significantly alter the arterial pressure of the patients studied. The values obtained were 92 ± 10.62, 88.9 ± 9.8, and 93.2 ± 11.1 mm Hg (mean ± SD) for groups I, II, and III, respectively.

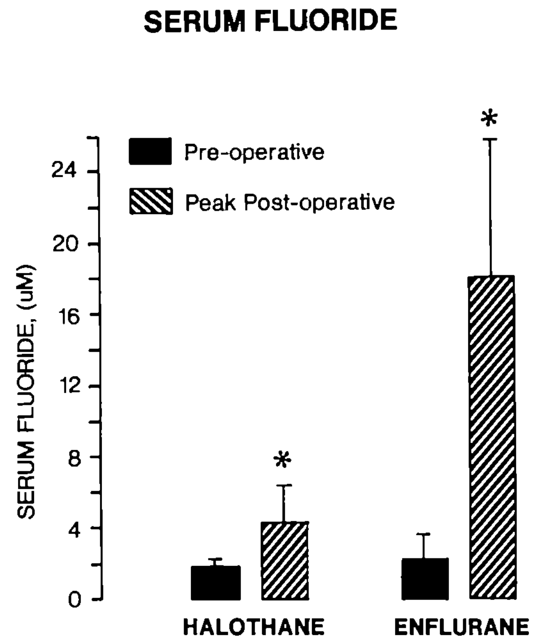

Figure 2. The peak postoperative concentration of serum inorganic fluoride (μM) occurred at 2 and 24 hr in the enflurane and halothane groups, respectively. Data are presented as mean ± SD of all patients studied (n = eight for each group). Asterisk indicates a statistically significant difference ($P < 0.025$*) in serum fluoride levels before and after anesthesia.

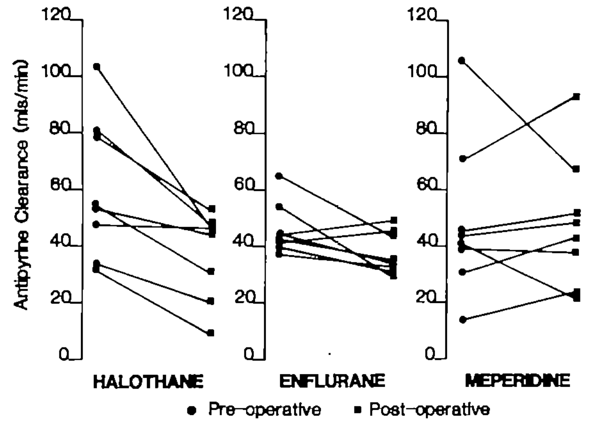

Figure 3. Antipyrine clearance was determined 24 hr before (●) and 48 hr after (■) exposure to either halothane, enflurane, or meperidine. Data are presented as the individual values for each patient. A statistically significant difference ($P < 0.02$) in antipyrine clearance before and after anesthesia was observed in the halothane group only.

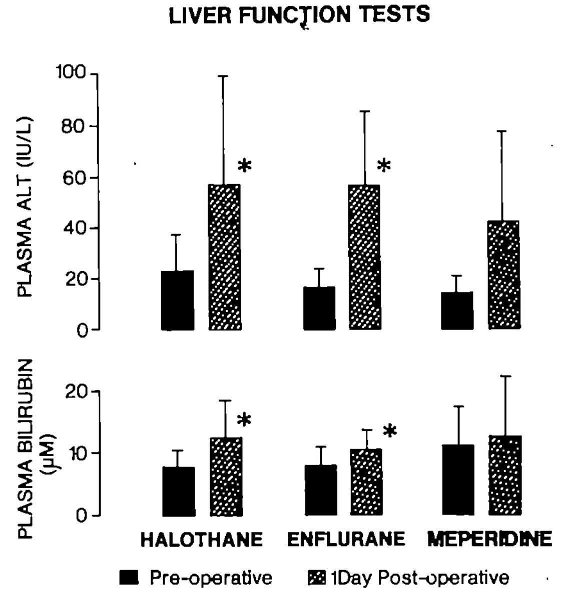

Figure 4. Plasma alanine aminotransferase (ALT) and plasma bilirubin were determined prior to and 24 hr following anesthesia. Data are presented as mean ± SD with n = eight patients in each group. *Statistically significant difference ($P < 0.05$) between levels before and after anesthesia.

Metabolite Formation

The volatile reductive metabolites (CDF and CTF) were detected in end-tidal air within 20 min of the commencement of halothane anesthesia and increased until a plateau was reached after approximately 60 min. The concentration of CTF was always greater than CDF and the cumulative mean ± SD from the 60–120-min samples was 0.36 ± 0.07 ppm and 0.11 ± 0.03 ppm for CTF and CDF, respectively.

The concentration of serum inorganic fluoride peaked 2 and 24 hr postoperatively in the enflurane and halothane groups, respectively. When compared with the preanesthetic values, the concentration of serum fluoride was found to have increased significantly ($P < 0.025$) after exposure to either halothane (group I) or enflurane (group II) (Fig. 2). In the 24-hr period after anesthesia, urinary fluoride excretion was significantly elevated ($P < 0.01$) in group II, i.e., the enflurane-exposed patients: 50 ± 51 before and 637 ± 284 μmol/24 hr after anesthesia (mean ± SD, n = 7) but unchanged in the halothane group, 58 ± 45 and 45 ± 23 μmol/24 hr (n = 6) for before and after anesthesia, respectively.

Antipyrine Pharmacokinetics

There was no significant difference between preoperative antipyrine terminal half-life, clearance, or volume of distribution when compared with the values of these parameters determined 48 hr after exposure in either the enflurane or meperidine groups. However, there was a significant decrease ($P < 0.02$) in antipyrine clearance, 60.6 ± 23.5 (mean ± SD) to 41.7 ± 20.4 ml/min (Fig. 3) and a corresponding increase ($P < 0.05$) in antipyrine half-life, 644 ± 220 to 1223 ± 784 min in patients exposed to halothane. No sig-

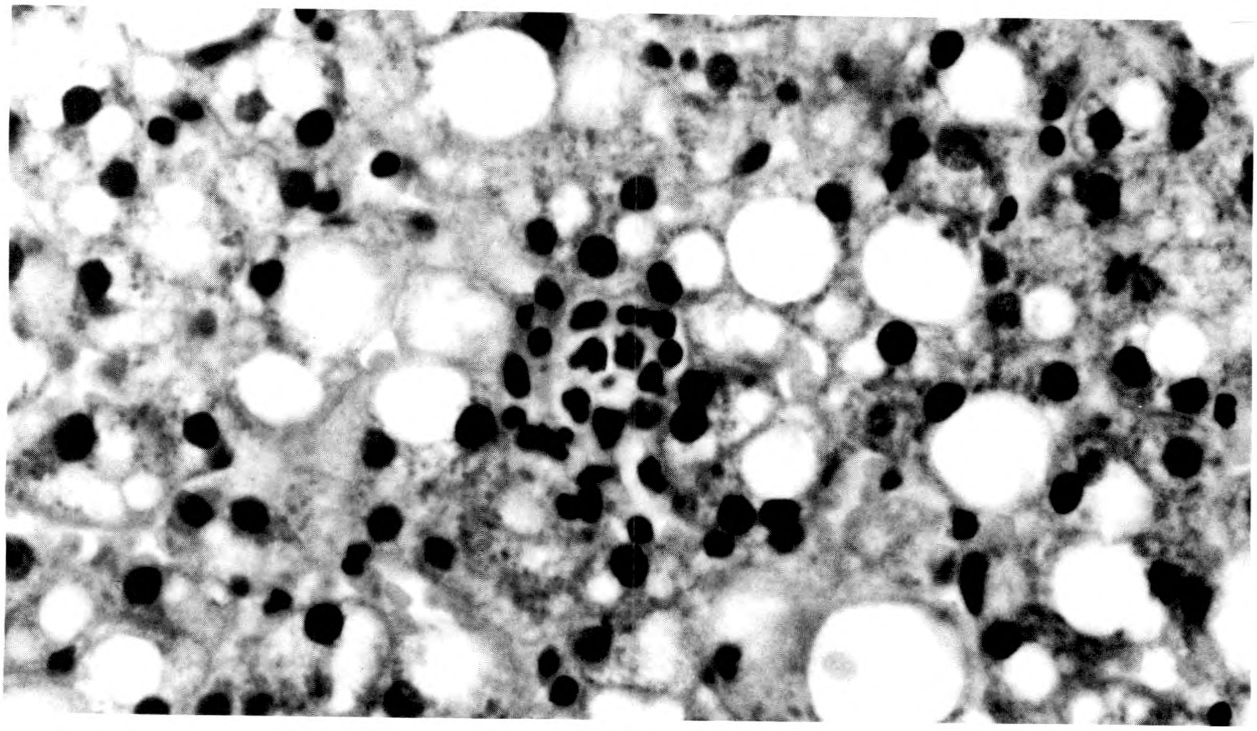

Figure 5. Liver biopsy from an obese patient, taken immediately after halothane exposure. The liver shows moderate fatty change. An aggregate of neutrophil leukocytes is seen in association with focal liver cell necrosis (center). Hematoxylin and eosin × 770.

nificant change occurred in the volume of distribution in these patients, 47.5 ± 9.5, before and 53.4 ± 17.7 L (mean ± SD) after anesthesia.

Liver Function Tests

After exposure to halothane, the postoperative concentrations (24 hr) of serum ALT (IU/L) and bilirubin (μM) were significantly elevated ($P < 0.05$) above preanesthetic values of 23 ± 25 IU/L and 7.8 ± 2.4 μM, respectively. A similar situation occurred in patients following the administration of enflurane, though neither serum ALT nor plasma bilirubin levels were changed postoperatively in patients given meperidine (Fig. 4).

Liver Histology

All of the liver biopsies showed some abnormality in liver morphology, but the same underlying pathology was apparent in each of the paired biopsies (from stages III and IV). The features seen included excessive amounts of lipofuscin and varying degrees of fatty change, portal fibrosis, and nonspecific reactive changes. None of the biopsies showed chronic hepatitis, cirrhosis, or malignancy. Biopsies from two group I patients and one group II patient, taken at the end of stage IV, showed several foci of liver cell necrosis with an associated neutrophil polymorphonuclear infiltrate situated in the vicinity of the central veins (Fig. 5). None of the stage IV biopsies showed hydropic swelling of centrilobular hepatocytes.

Liver Morphometry

The average nuclear and hepatocyte areas in the central vein regions before anesthesia were similar to hepatocyte and nuclear areas after either enflurane or halothane (Table 3). (Because of the cost and time involved, morphometric studies were not performed on biopsies from patients supplemented with meperidine (group III).) No significant differences were observed in either hepatocyte or nuclear areas between the central vein or portal tract regions. The average cell and nuclear areas of hepatocytes within portal tract regions were 507.8 ± 139 μm^2 and 67.3 ± 15 μm^2 (mean ± SD), respectively. Mean volume of mononucleate hepatocytes was calculated to be 9400 μm^3 and the volume of an average hepatocyte nucleus approximately 720 μm^3.

Discussion

In the present study, the changes observed in liver function tests after either halothane or enflurane were

Table 3. Liver Morphometry

	Nuclear area (μm^2)	Hepatocyte area (μm^2)
Enflurane		
Patient 1—pre	68.5 ± 15	543.1 ± 185
—post	87.1 ± 23	538.0 ± 147
Patient 2—pre	76.3 ± 31	581.8 ± 216
—post	81.4 ± 23	646.7 ± 224
Patient 3—pre	77.3 ± 23	526.6 ± 178
—post	58.7 ± 15	563.7 ± 201
Patient 4—pre	65.4 ± 15	528.2 ± 147
—post	64.4 ± 15	476.7 ± 154
Halothane		
Patient 5—pre	80.6 ± 15	466.3 ± 147
—post	65.1 ± 15	422.3 ± 132
Patient 6—pre	66.2 ± 15	433.1 ± 138
—post	56.3 ± 15	450.7 ± 123
Patient 7—pre	67.3 ± 15	552.4 ± 186
—post	94.6 ± 31	599.9 ± 139
Patient 8—pre	58.9 ± 15	429.8 ± 100
—post	68.2 ± 8	465.5 ± 147

Data are presented as the mean ± SD of 60 hepatocytes.

comparable, suggesting that the extent of hepatocellular dysfunction was essentially the same after each agent. However, plasma ALT and serum bilirubin values may be increased independently of the anesthetic agent, e.g., following intra-abdominal surgery (22) or the administration of either thiopental or propanidid (23). In previous studies, the postoperative measurement of such enzymes as ALT and serum ornithine carbamyl transferase has indicated that there were no differences when comparing halothane, methoxyflurane, or spinal anesthesia (6), halothane or enflurane (8), or between narcotic anesthesia, halothane, and methoxyflurane (7). Other factors may also cause mild hepatocellular damage, e.g., sepsis, hypotension, severe hemolysis, and surgical manipulation. In this study, these factors appeared not to be implicated, cardiovascular changes were monitored continuously and were comparable in all groups, and no patient developed postoperative sepsis nor was there evidence of severe hemolysis. If changes in plasma ALT and bilirubin in groups I and II were in response to surgical manipulation, then elevated levels would be expected to have occurred in group III, i.e., patients receiving meperidine. The results of this study suggest that there may be a greater propensity for transaminase levels to increase after halogenated anesthetic agents than after opioid anesthesia, and that these changes may be unrelated to extraneous circumstances. In addition, only halothane anesthesia was associated with decreased postoperative clearance of the "capacity limited" drug antipyrine.

Clearance of ICG has been used as an indirect index of hepatic blood flow (24). After intravenous administration, ICG is selectively taken up by hepatic parenchymal cells, undergoing negligible renal, pulmonary, peripheral tissue, or cerebrospinal uptake. Surgical trauma is known to decrease hepatic blood flow (as determined by a colloidal gold technique) (25); therefore, changes in the hepatic extraction of a high clearance compound such as ICG would be expected to be observed during surgery. Statistical analysis of the results of this study verified that surgical stimulation constituted the major effect in decreasing C_{ICG} in all groups when comparing stage III and stage I. These results are in contrast to a recent study that reported that ICG clearance was not reduced in patients receiving halothane and undergoing peripheral surgery (26). Direct comparison of that study with the results reported here is not possible owing to the dissimilar nature of the surgical procedures, i.e., abdominal versus peripheral and the dose of halothane administered, 0.5% as opposed to 0.35%.

Halothane is metabolized in the liver by both oxidative and reductive pathways (18,27). The latter is considered to be associated with greater potential for hepatotoxicity and the volatile reductive metabolites CTF and CDF have been demonstrated in both humans and an animal model (17,18). In the animal model, the formation of the reductive metabolites, including free radicals (28), was associated with increased serum ALT concentration and centrilobular necrosis. These studies provided evidence that halothane metabolism can cause direct hepatocellular injury.

In the present study, the postoperative excretion of urinary fluoride was significantly increased in the enflurane group (mean 640 μmol/24 hr) but was unchanged from baseline values in the halothane patients (mean 45 μmol/24 hr). The uptake of inorganic fluoride by bone (29) can reduce the amount of fluoride available for urinary excretion. In view of the lesser amount of fluoride formed in the halothane patients, bone absorption may account for the lack of increase observed in urinary fluoride in the halothane group. In contrast, significantly elevated serum fluoride values were found in patients exposed to either halothane or enflurane. Inorganic fluoride is a metabolite of enflurane and the highest values obtained were well below the level considered to be potentially nephrotoxic in humans, 50 μmol/L (30). The finding of increased serum fluoride levels, however, is of more concern in patients exposed to halothane. The reductive pathway of halothane metabolism results in the formation of inorganic fluoride and the volatile metabolites CDF and CTF. An association between the extent of reductive metabolism and the amount of bound hepatic organic fluoride has been reported to occur in obese patients (31) and it has subsequently been shown that serum fluoride is also increased in this group of patients (32). The presence of obese patients in the halothane group may have contributed to the elevation in serum fluoride, in comparison with studies in nonobese patients where even prolonged halothane anesthesia did not result in elevated serum fluoride (33). Indirect support for this is provided by studies in rats that reported that obesity increased serum fluoride after enflurane and isoflurane anesthesia (34). Sharp et al. (35) and Gourlay et al. (17) have reported elevations of the levels of CDF and CTF in both obese and nonobese patients. The presence of CDF and CTF in the exhaled breath of all patients anesthetized with halothane suggests that free radical intermediates may be formed in humans. The level of CTF in this study was consistently higher than that of CDF and, therefore, the elevation observed in serum fluoride may have been a reflection of the defluorination of CDF (36).

Antipyrine metabolism is highly reproducible within a given individual, and thus the pharmacokinetics of antipyrine disposition has been used extensively in humans to assess the in vivo functional integrity of the hepatic microsomal mixed-function oxidase system following a single environmental perturbation (12). In this study, antipyrine kinetics were studied in patients before and after anesthesia. In two groups of patients (enflurane and meperidine), no significant changes were observed in the volume of distribution, clearance, or terminal half-life of antipyrine when comparing data collected before and after anesthesia. These results are in accord with a previous report in which enflurane was found to have no effect on antipyrine metabolism in a group of 18 surgical patients (37). Enflurane metabolism in vivo is not inducible by phenobarbital (38); in contrast, the metabolism of both antipyrine and halothane is enhanced (12,18). The results of this study suggest that antipyrine may be metabolized by cytochrome P-450 isoenzymes distinct from those that defluorinate enflurane. In support of this concept, the elimination rate of antipyrine has been shown not to correlate with the individual's capacity to metabolize enflurane (37,39).

In those patients receiving halothane, a significant decrease in antipyrine clearance was observed 48 hr after anesthesia, and this was reflected in a corresponding increase in the half-life. Other studies, in contrast to these findings, found that antipyrine clearance was significantly increased in patients when determined either 4 or 8 days (40) and 7 days (41) after surgery and after exposure to trace concentrations of halothane for 10 days (42). Similar to enflurane, no correlation could be established between antipyrine pharmacokinetic parameters in individuals and their ability to debrominate halothane (43).

Changes in antipyrine disposition viewed as a solitary entity may be interpreted as a consequence of numerous environmental factors, e.g., surgery, bed rest, diet, stress (12). However, the fact that a decreased metabolic clearance was observed in only one group of patients studied, coupled with elevated plasma fluoride levels and exhalation of reductive halothane metabolites, suggests that the changes in antipyrine disposition may be a result of a specific inhibition/destruction of the drug metabolizing enzyme system as a result of possible free radical production during halothane anesthesia. A recent study in a rat model of halothane-associated hepatoxicity demonstrated that decreases in cytochrome P-450 content and aminopyrine demethylase activity occur under conditions that promote the reductive metabolism of halothane (44). In addition, Trudell et al. (45) have reported the formation of a free radical in vitro by human cytochrome P-450 following incubation with halothane.

Three of the 24 biopsies taken at the end of stage IV showed occasional foci of acute liver cell necrosis in the vicinity of the central veins. Two of the patients had received halothane, and of these one had a moderately fatty liver (obese patient) and the other had nonspecific reactive changes. The third patient, who was obese and received enflurane, had only mild fatty change in the liver biopsy. All three had postoperative elevations of plasma ALT above the normal range and one halothane patient also had an elevated bilirubin level. Acute liver cell necrosis is well recognized in liver biopsies taken after abdominal surgery and is seen after a wide variety of volatile and nonvolatile anesthetic agents; the injury is though to be due to intrahepatic hypoxia rather than direct hepatic trauma (46).

Three other group I patients (two obese), five other group II patients (one obese), and three group III patients (one obese) also had postoperative elevation of plasma ALT above normal but did not have acute liver cell injury recognizable by light microscopy. Only one of the seven obese patients studied did not have a postoperative elevation of ALT above normal, although in this one patient both liver biopsies showed marked fatty change. There was no obvious correlation between the nature and severity of the underlying liver pathology and the extent of the postoperative ALT elevation.

Hepatocytes in the region of the central veins contain more smooth endoplasmic reticulum (SER) and cytochrome P-450 than hepatocytes in other regions of the liver lobules (47); heterogeneity of liver cell structure and function is thought to be an important factor in the pathogenesis of drug hepatotoxicity. Early, experimental liver cell injury associated with agents such as halothane is seen in the centrilobular region of the liver and liver cell enlargement due to hydropic degeneration is one of the early manifestations of injury. However, our morphometric study did not reveal any change in hepatocyte size after anesthesia with either halothane or enflurane. The results demonstrated that hepatocyte and nuclear sizes are consistent across the lobule of the human liver. The values of hepatocyte and nuclear volumes in the present study are comparable to those of Rohr et al. (48), who reported hepatocyte and nuclear volumes of 11,000 μm^3 and 800 μm^3, respectively.

It is possible that structural changes may have occurred but they were not visible by light microscopy. A recent ultrastructural study described swelling of rough endoplasmic reticulum (RER) and proliferation of smooth endoplasmic reticulum (SER) in all seven patients who received halothane; a similar change also was seen in one of five patients who received enflurane. These changes were not seen in any of the patients who received nitrous oxide–barbiturate–opioid anesthesia (49). The authors did not state whether they compared cells from the centrilobular regions before and after anesthesia; liver biopsies showing underlying pathology were excluded from their study. Swelling of RER and proliferation of SER were considered to be toxic changes, although the latter may be observed following exposure to a variety of drugs. A carefully designed morphometric study of ultrastructural changes in "normal" livers after halothane anesthesia is needed to determine whether "toxic changes" do indeed occur.

In summary, this study demonstrates that reductive biotransformation of halothane (as evidenced by the formation of the metabolites CDF, CTF, and inorganic fluoride) occurs in patients undergoing routine anesthesia with halothane under conditions of normoxia. Although the patients studied did not develop clinical evidence of jaundice, the results suggest that reductive metabolism, albeit to a minor extent, is associated with transient changes in hepatocellular function.

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Effects of a Specific Benzodiazepine Antagonist (RO 15-1788) on Cerebral Blood Flow

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FORSTER A, JUGE O, LOUIS M, MAHORY A. Effects of a specific benzodiazepine antagonist (RO 15-1788) on cerebral blood flow. Anesth Analg 1987;66:309–13.

RO 15-1788, a specific benzodiazepine antagonist, although it effectively antagonizes the clinical effects of benzodiazepines (i.e., sedation and amnesia), can also induce subjective agonist effects such as sedation or inverse agonist effects such as anxiety. The purpose of this study was to investigate in seven healthy volunteers the effect of RO 15-1788 on cerebral blood flow when intravenously injected alone or with midazolam and to compare its effects with midazolam administered alone. Cerebral blood flow was measured with the ^{133}xenon inhalation technique and the drugs were administered simultaneously in a double-blind, randomized fashion during the four following sessions: 1) placebo–placebo; 2) midazolam–placebo; 3) RO 15-1788–placebo; 4) midazolam–RO 15-1788. No difference in cerebral blood flow was noted between the placebo–placebo, the RO 15-1788–placebo, and the RO 15-1788–midazolam sessions—although midazolam injected alone decreased cerebral blood flow by 30%. The sedation, amnesia, and the electroencephalograph (EEG) and muscle tone changes observed with midazolam–placebo were not present during the RO 15-1788–placebo and RO 15-1788–midazolam sessions. This study demonstrates the absence of effects of RO 15-1788 on cerebral blood flow when injected alone and the efficacy of this new drug in antagonizing the depressant effects of midazolam on cerebral hemodynamics.

Key Words: HYPNOTICS, BENZODIAZEPINE—antagonist. ANTAGONISTS, MISCELLANEOUS—benzodiazepines. BRAIN—blood flow.

Benzodiazepines are known to produce in humans (1–3) and in animals (4–5) a decrease in cerebral blood flow (CBF) that is related to a reduction in cerebral oxygen consumption ($CMRO_2$) (4,6). In clinical practice, since benzodiazepines have cerebrovascular properties similar to those of barbiturates, they are administered as an alternative to induction of anesthesia in patients with increased intracranial pressure or to sedation in neurosurgical intensive care patients.

Recently, a new class of benzodiazepines, the imidazodiazepines, was developed that have specific benzodiazepine antagonist properties. Among these, RO 15-1788 (RO) was selected for clinical trials (7).

The efficacy of RO in antagonizing the agonist effects of benzodiazepines (e.g., sedation or amnesia) has been demonstrated in humans (8,9) without important side effects. However, inverse agonist effects of the drug, such as anxiety, have been described in humans (10) as well as in animals (11). Subjective slight agonist effects of RO have also been noted in human studies (9,12) but objectively demonstrated in animal studies only (13).

The evaluation of the cerebrovascular effects of RO is clinically relevant: if RO decreases or does not change CBF, it could be safely administered in neurosurgical patients to reverse benzodiazepines at the end of an operation or to allow differential diagnosis of a coma in which benzodiazepines could be implicated; if RO increases CBF, it would be contraindicated in patients with potentially increased intracranial pressure.

The purpose of the present study is to evaluate the effect of RO on CBF, when administered alone or in association with midazolam, in order to determine, first, if RO antagonizes the decreased CBF induced by midazolam and, second, if the subjective side effects observed after administration of RO alone (anxiety/dizziness) were associated with changes in CBF.

Patients and Method

Seven healthy male volunteers, mean age 36 ± 5 yr (mean ± SD) and mean weight 73 ± 9 kg, were studied after informed consent and approval of the protocol by the Committee of Ethics in Human Research

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Table 1. EEG and EMG Findings After Administration of the Drugs

	Placebo + placebo	Midazolam + placebo	RO + placebo	Midazolam + RO
EEG amplitude (μV)	45.1 ± 16	28 ± 9*	46 ± 10	43 ± 19
f EEG (Hz)	10.1 ± 1.1	16.8 ± 2.0*	11.1 ± 2.3	10.0 ± 1.5
EMG (μV)	68 ± 16	15 ± 11*	67 ± 10	68 ± 16
Depth of sleep	Stage 0	Stage II	Stage I	Stage I
n	7/7	7/7	3/7	2/7

Abbreviations: f EEG, frequency of electroencephalographic waves; EMG, electromyogram.
*$P < 0.01$ when compared with three other sessions.

of our institution were obtained. Each subject was studied during four sessions that were randomized and separated by at least 3 days. During each session, subjects simultaneously received, in a double-blind fashion, two drugs in two different intravenous lines at the dosages indicated as follows:

Session 1: Placebo and placebo (10 ml NaCl 0.9%).

Session 2: Midazolam (0.15 mg/kg diluted in 10 ml NaCl 0.9%) and placebo.

Session 3: RO (0.1 mg/kg diluted in 10 ml NaCl 0.9%) and placebo.

Session 4: Midazolam (0.15 mg/kg) and RO (0.1 mg/kg).

Electrocardiogram and end-tidal CO_2 (FE_{CO_2}) were continuously monitored throughout the study. Arterial blood pressure was measured each minute with a noninvasive automatic device (Dinamap®). The CBF was measured with the ^{133}xenon inhalation technique (14). Twenty-four ^{133}xenon detection probes were used, fixed on a plastic helmet directed toward both the middle cerebral artery and the posterior cerebral artery distribution bilaterally.

Using a closed breathing circuit, 4–5 mCi of ^{133}xenon was inhaled through a face mask during a 1-min saturation period. An open circuit was utilized during the desaturation period, which lasted 10 min.

End-tidal ^{133}xenon was monitored by continuous aspiration of gas samples through a small catheter placed within the mask at the rate of 1.5 L/min. The same catheter was also used for end-tidal CO_2 measurements.

The CBF was averaged from the 24 desaturation curves from which were calculated F_1, which represents the fast compartment flow, and the ISI_2 (initial slope index of Risberg), which represents a combination of fast and slow flow compartments (14).

For technical reasons, CBF could not be measured in subject 7 when given RO and placebo or in subject 4 when given midazolam and RO. Because of an irregular breathing pattern induced by midazolam, F_1 could not be calculated in subjects 3 and 5 during the midazolam–placebo session.

To measure sleep during the experiment without stimulating the subjects, a six-lead electroencephalogram (EEG) was continuously recorded and the changes induced by the different drugs were evaluated in a blinded fashion as the depth of sleep (15) as follows:

Stage 0: Wakefulness; low voltage and mixed frequency

Stage I: Appearance of alpha waves

Stage II: Appearance of sleep spindles and k complex

Stage III–IV: Appearance of delta waves

Stage V: REM sleeplike Stage I plus sawtooth waves

An electromyogram (EMG) electrode was applied on the chin of each subject in order to evaluate changes in jaw muscle tone.

At the end of the CBF measurements, neurobehavioral status and anterograde amnesia were evaluated and the subjects were encouraged to describe their feelings. The degree of sedation was subjectively assessed by one of the authors as follows:

1. Subject spontaneously awake.
2. Subject sleepy but rousable on verbal command.
3. Subject sleepy but rousable on tactile stimulation.
4. Subject asleep and unarousable.

Anterograde amnesia, defined as a lack of recall of a three-digit number and of an object presented to the subject 1 min earlier, was evaluated every 2 min.

The volunteers fasted at least 6 hr before the study, which always took place at the beginning of the afternoon. Once the subjects were placed in the supine position, with the cardiac monitoring in place, a small IV cannula was inserted in each hand and a perfusion of NaCl 0.9% running at the rate of 100 ml/hr was started. A mask that allowed inhalation of ^{133}xenon and monitoring of end-tidal CO_2 was then applied on the volunteer's face. After a 10-min adaptation period, two of the three drugs studied were injected over a 15-sec period, one in each hand, according to the sessions. Two minutes after the injections, CBF measurements were started.

Table 2. Baseline Values and Largest Changes (Δ) in Mean Arterial Blood Pressure, Heart Rate, and $\mathrm{FE}_{\mathrm{CO}_2}$ After Administration of the Drugs

	Placebo + placebo	Midazolam + placebo	RO + placebo	Midazolam + RO
Baseline (mm Hg)	86 ± 7	89 ± 7	85 ± 8	85 ± 6
$\Delta\overline{\mathrm{BP}}$	−3 ± 0.5	−10 ± 4[a]	−3 ± 4	−3 ± 5
Baseline (bts/min)	68 ± 12	66 ± 7	64 ± 2	69 ± 12
ΔHR	−1 ± 1.5	+7 ± 3[b]	−5 ± 2[b]	+1 ± 10
Baseline (mm Hg)	41 ± 3	40 ± 5	41 ± 4	40 ± 4
$\Delta\mathrm{FE}_{\mathrm{CO}_2}$	+1 ± 0.2	+3.5 ± 0.3[a]	+1.5 ± 0.2	+1 ± 1.0

Abbreviations: $\overline{\mathrm{BP}}_{\mathrm{BP}}$, mean arterial blood pressure; HR, heart rate.
[a] $P < 0.05$, statistically different from baseline value.
[b] $P < 0.01$, statistically different from baseline value.

All the data are expressed as means ± SD. The data between the different sessions were compared with a one-way analysis of variance for repeated measurements and the differences were detected with the test of Duncan, $P < 0.05$ being considered statistically significant.

For the CBF measurements, analysis of variance for repeated measurement was performed only with the variables obtained during the four sessions for all the subjects; i.e., three volunteers for F_1 and five for ISI_2.

Results

Neurobehavioral Status

During the midazolam–placebo session, at the end of CBF measurements, all subjects were sleepy but rousable on verbal command and had anterograde amnesia that lasted 53 ± 15 mins. During the three other sessions, none of the subjects were asleep at the end of the experiment, nor did they have the feeling of having slept; memory tests showed no anterograde amnesia in any of the volunteers. Retrograde amnesia was never noted throughout the study; all the volunteers were able to describe the events occurring in the investigation room before the injections. However, when RO was administered alone or in association with midazolam, all subjects expressed a feeling of anxiety and slight discomfort, such as dizziness.

EEG and EMG

Changes in EEG and EMG are indicated in Table 1. Muscle tone decreased in six of the seven volunteers during the midazolam–placebo session (the mean amplitude passing from 68 ± 16 μV to 15 ± 11 μV). It remained stable when placebo and RO were administered alone and decreased only in one subject when midazolam was associated with RO. All the subjects were in sleep stage II during the midazolam–placebo session whereas, when RO was administered alone, four volunteers were in stage 0 and three in stage I, and when RO was given with midazolam, five were in stage 0 and two in Stage I. A significant increase in EEG frequency and decrease in EEG amplitude were noted only during the midazolam–placebo session; during the RO–placebo and midazolam–placebo sessions, no changes from baseline were observed.

Hemodynamic and $\mathrm{FE}_{\mathrm{CO}_2}$

The hemodynamic and $\mathrm{FE}_{\mathrm{CO}_2}$ data measured during the four sessions are summarized in Table 2 where the baseline values and the biggest changes observed are indicated. The baseline data were similar in all groups, with the only significant changes in blood pressure and $\mathrm{FE}_{\mathrm{CO}_2}$ occurring during the midazolam–placebo session, where mean arterial blood pressure decreased by 10 ± 4 mm Hg and $\mathrm{FE}_{\mathrm{CO}_2}$ increased by 3.5 ± 0.3 mm Hg. Heart rate increased significantly only in the midazolam–placebo session and decreased significantly when RO was associated with placebo.

Cerebral Blood Flow

Individual and mean CBF data are presented in Table 3. When compared with the placebo–placebo session, the only significant changes ($P < 0.01$) were noted in the midazolam–placebo session when F_1 decreased in all subjects (mean decrease 34%) and ISI_2 in six of the seven volunteers (mean decrease 22%). RO alone produced variable individual changes, with a slight increase in CBF observed in subjects 1 and 3 and a slight decrease in subjects 2–4, and with CBF remaining stable in subjects 5 and 6; mean values of

Table 3. Individual and Mean CBF Values After Administration of Placebo, Midazolam (0.15 mg/kg), RO 15-1788 (0.1 mg/kg), or a Combination of Midazolam and RO 15-1788

	Placebo–placebo		Midazolam–placebo		RO–placebo		Midazolam–RO	
Subjects	F_1	ISI_2	F_1	ISI_2	F_1	ISI_2	F_1	ISI_2
1	49.0	36.0	25.5	22.5	56.0	43.0	45.0	33.0
2	60.0	46.0	29.0	25.0	45.5	40.0	73.0	51.5
3	43.5	36.5	—	30.0	55.0	44.5	50.5	42.0
4	55.0	41.0	45.5	40.0	51.0	38.0	—	—
5	74.0	53.0	—	45.0	75.0	53.0	73.5	57.0
6	59.0	42.5	42.0	37.0	65.5	43.0	69.0	45.0
7	73.0	54.0	54.5	40.5	—	—	67.0	55.0
Mean	59.1	44.1	39.3[a]	34.3[a]	58.0	43.6	63.0	47.3
± SD	±11.4	±7.3	±12.0	±8.5	±10.6	±5.2	±12.0	±9.0
n	7	7	5	7	6	6	6	6

Abbreviations: F_1 (ml·100 g^{-1}·min^{-1}), fast compartment flow; ISI_2, initial slope index.
[a] Statistically different ($P < 0.01$) from other groups.

CBF after RO alone or placebo thus were similar. The association of midazolam and RO also produced minimal changes; a slight increase in CBF was noted in five subjects and a slight decrease in one volunteer.

Discussion

The present study confirms the decrease in CBF produced by midazolam (3) and the efficacy of RO in antagonizing the clinical (8,4) and EEG (16) effects of midazolam. The absence of a decrease in CBF after midazolam in subject 4 is probably related to the relatively high increase in FE_{CO_2} (+6 mm Hg) in that patient. When RO was associated with midazolam, none of the subjects became clinically sleepy or suffered from amnesia, and the increase in EEG frequency typically observed with midazolam alone (17) was not noted. However, three of seven patients after RO alone and two of seven after the association of RO–midazolam were in a Stage I of sleep according to the EEG whereas no volunteer was considered asleep after placebo. Although not statistically significant, these results are in contradiction to recent EEG studies showing that RO alone has a central activating effect (18). Our data also confirm the absence of cardiorespiratory effects of RO (9,10), since blood pressure and FE_{CO_2} changes with RO were similar to those seen with placebo. However, RO did prdduce a significant decrease in heart rate when compared with placebo.

Our results demonstrate that RO does not influence CBF when injected alone, but totally antagonizes the depressive effect of midazolam on CBF, since during the RO–midazolam session CBF values were similar to those obtained during placebo–placebo. The latter results are similar to experimental data, demonstrating that RO or 3-hydroxymethyl-β-carboline, another benzodiazepines antagonist, reverses the decrease in CBF produced by benzodiazepines (19,20) but are in contradiction to a recent study showing that physostigmine, which is known to reverse the sedation induced by benzodiazepines, or 3-carbo-*t*-butoxy-β-carboline, another benzodiazepine antagonist, increases CBF and $CMRO_2$ in rats (21). The mechanism by which physostigmine produces its effect is still debated, but is understandable for β-carboline since this compound has an inverse agonist activity (22).

Surprisingly, the discomfort and anxiety produced by RO when injected with placebo, which can be considered an inverse agonist effect, were not associated with an increase in CBF, blood pressure, or heart rate. Similar observations have been noted in other studies, where intolerable anxiety after administration of RO did not produce changes in heart rate, blood pressure, or cardiac output (10), or where the action of midazolam on plasma catecholamine levels was reversed by RO without affecting hemodynamic stability (23).

The clinical implication of this study is that the administration of RO to reverse the effects of benzodiazepines on CBF may be safe in patients whose intracranial pressure was normal before the administration of benzodiazepines, since after reversal of midazolam, CBF values were similar to those obtained after placebo. Nevertheless, in patients with a poor intracranial compliance who have benefited from the cerebrovasoconstriction effect of benzodiazepines, RO could induce intracranial hypertension due to an increase in intracranial blood volume as CBF returns to values that existed prior to the administration of the benzodiazepines.

The above applies to patients who have received benzodiazepines for only a short period, whereas in patients chronically treated with benzodiazepines, RO may provoke benzodiazepine withdrawal symptoms

(24), including epileptic seizures (25), that could increase CBF to values greater than those measured before administration of benzodiazepines.

It seems likely that RO will reverse the CBF effects of other benzodiazepines, since it has been shown to be clinically effective with diazepam or flunitrazepam (25,4). However, further studies are needed to determine the effect of RO on intracranial pressure in patients acutely and chronically treated with benzodiazepines.

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Alcuronium Pretreatment Attenuates Succinylcholine-Induced Increases in Plasma Catecholamine Concentrations in Humans

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OSHITA S, TAMURA H, MASUDA T, FUKUDA S, TAKESHITA H. Alcuronium pretreatment attenuates succinylcholine-induced increases in plasma catecholamine concentrations in humans. Anesth Analg 1987;66:314–6.

The effect of alcuronium given before succinylcholine (SCh) on plasma catecholamine concentrations, systolic blood pressure and heart rate was studied in patients anesthetized with enflurane. Twenty-one patients were divided into three groups; six control patients without SCh, eight SCh (1 mg/kg) patients, and seven pretreated patients given alcuronium, 0.04 mg/kg, 5 min before SCh, 1 mg/kg. In the SCh group, mean plasma norepinephrine concentrations, systolic blood pressure, and heart rate significantly increased with onset of fasciculations, whereas in the pretreated patients these variables did not change significantly and no fasciculation was observed. These results indicate that alcuronium pretreatment significantly attenuates the SCh-induced increases in plasma norepinephrine concentrations, systolic blood pressure and heart rate.

Key Words: NEUROMUSCULAR RELAXANTS—succinylcholine, alcuronium. SYMPATHETIC NERVOUS SYSTEM—catecholamines.

Among cardiovascular side effects of neuromuscular blocking agents, an increase in blood pressure and/or heart rate secondary to succinylcholine (SCh) administration has considerable clinical importance in certain patients. Although it has been reported that alcuronium given before SCh attenuates an increase in blood pressure in response to intubation with an aid of SCh (1), the study did not elucidate whether alcuronium pretreatment modified the effects of SCh alone or the combined effects of SCh and intubation on sympathetic activity. The present study was designed to examine the effects of alcuronium pretreatment on SCh-induced increases in plasma catecholamine concentrations, systolic blood pressure and heart rate.

Methods

This study was approved by the hospital committee on ethics. Twenty-one patients scheduled for elective surgery (ages 20–60 yr), without symptomatic neuromuscular or cardiovascular disease, were randomly assigned into one of three groups: six patients received intravenous physiologic saline, 3 ml (saline group); eight patients received intravenous SCh, 1 mg/kg (SCh group); seven patients received intravenous alcuronium, 0.04 mg/kg, 5 min before SCh, 1 mg/kg (pretreatment group).

Premedication consisted of scopolamine, 0.008 mg/kg, given intramuscularly 30 min before induction of anesthesia. Prior to induction, under local anesthesia with 0.5% lidocaine, 22-gauge catheters were placed both in the superficial dorsal vein for infusion of drugs and lactated Ringer's solution and in the radial artery for collection of blood samples. Anesthesia was induced with thiopental, 3 mg/kg, followed by inhalation of 3% enflurane in oxygen. Ventilation was controlled without intubation throughout the study. The time between the administration of thiopental and that of either saline or SCh was 15 min in all groups. Samples of arterial blood for measurement of plasma norepinephrine (NE) and epinephrine (E) concentrations were drawn immediately before (baseline) and 1, 4 and 10 min after SCh. At the same time intervals, systolic blood pressure and heart rate were measured. Samples for the analyses of plasma catecholamine concentrations (5 ml) were immediately placed in capped containers with EDTA·2Na, then stored on ice and centrifuged within 15 min. The decanted plasma was stored at −40°C until analyzed

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Table 1. Arterial Blood Gas Tensions and Plasma Enflurane and Potassium Concentrations

	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pH	Plasma enflurane concentrations (mg/dl)	Plasma potassium concentrations (mEq/L)
Saline group ($n = 6$)					
Baseline	587 ± 28	38 ± 1	7.39 ± 0.01	15.7 ± 0.6	3.4 ± 0.1
4 min	566 ± 26	40 ± 1	7.38 ± 0.01	15.9 ± 0.4	3.6 ± 0.1
10 min	544 ± 29	41 ± 1	7.37 ± 0.01	16.6 ± 0.9	3.6 ± 0.1
SCh group ($n = 8$)					
Baseline	558 ± 22	36 ± 2	7.43 ± 0.02	15.5 ± 1.5	3.6 ± 0.1
4 min	568 ± 24	40 ± 4	7.41 ± 0.03	16.4 ± 1.4	3.9 ± 0.2
10 min	545 ± 31	39 ± 4	7.41 ± 0.03	17.1 ± 1.4	4.0 ± 0.2
Pretreatment group ($n = 7$)					
Baseline	577 ± 17	36 ± 1	7.38 ± 0.02	17.0 ± 1.2	3.6 ± 0.1
4 min	564 ± 18	40 ± 2	7.35 ± 0.02	17.2 ± 1.6	3.7 ± 0.1
10 min	545 ± 18	38 ± 2	7.35 ± 0.02	18.0 ± 1.6	3.8 ± 0.1

Values are means ±SEM.

for NE and E using high-performance liquid chromatography (Shimadzu LC-1, Japan) with electrochemical detection (Bioanalytical System LC3A, USA) (2). Briefly, this method used 200 pg dihydroxybenzylamine as an internal standard and the catecholamines were eluted with 0.1 M perchloric acid. The lower limit of detection of the assay for the catecholamines was approximately 20 pg/ml, with an overall coefficient of variation of 5–10%. Arterial samples (3 ml) for the analyses of blood gas tensions and plasma enflurane and potassium concentrations were collected in separate syringes immediately before (baseline), and 4 and 10 min after SCh.

Statistical analysis was performed using the one-way analysis of variance (ANOVA, F ratio) with critical-difference testing. $P < 0.05$ was considered statistically significant.

Results

The three groups were similar with respect to sex distribution and age. The results of blood gas analyses, plasma enflurane and potassium concentrations, plasma NE and E concentrations, systolic blood pressure and heart rate are shown in the tables. There were no significant differences from baseline in the factors known to cause changes in plasma catecholamine concentrations, i.e., PaO_2, $PaCO_2$, plasma enflurane, and potassium concentrations, suggesting that these variables remained stable throughout the study (Table 1).

As shown in Table 2, in the SCh group, the mean plasma NE concentrations increased and reached the maximum ($P < 0.05$) at 4 min, then declined to the baseline levels 10 min after SCh. The mean plasma E concentrations also increased, but the change did not reach statistical significance. The mean systolic blood pressure and heart rate increased after SCh and reached the maximum ($P < 0.05$) at almost the same time that fasciculations became fully developed, i.e., approximately 1 min after SCh. In contrast, there were no significant increases in plasma catecholamine concentrations, systolic blood pressure and heart rate, and no fasciculation occurred in response to SCh in the pretreatment group.

Discussion

Our results show that alcuronium pretreatment significantly attenuates the SCh-induced increases in plasma NE concentrations, systolic blood pressure, and heart rate. It is known that SCh, like acetylcholine, has a transient agonistic with a subsequent desensitizing action on the nicotinic receptors, and that alcuronium competitively blocks the action of acetylcholine on nicotinic receptors (3,4). Although nicotinic receptors distribute in the central nervous system, adrenal medulla, neuromuscular junction and sympathetic ganglia (3), it is unlikely that nicotinic receptors of the central nervous system and adrenal medulla played a significant role in the increases in plasma NE concentrations observed in the SCh group of the present study. This belief may be supported by the following facts. SCh has no effect on the central nervous system because of its inability to penetrate the blood-brain barrier in normal adults (4), and also has no effect on catecholamine release from isolated bovine adrenal medulla (see Figure 6 of reference 5).

SCh-induced fasciculations and the significant increases in systolic blood pressure and heart rate, both

Table 2. Plasma Norepinephrine and Epinephrine Concentrations, Systolic Blood Pressure, and Heart Rate

	Plasma norepinephrine concentrations (pg/ml)	Plasma epinephrine concentrations (pg/ml)	Systolic blood pressure (mm Hg)	Heart rate (beats/min)
Saline group ($n = 6$)				
Baseline	196 ± 42	62 ± 11	92 ± 4	79 ± 3
1 min	200 ± 39	66 ± 16	92 ± 3	77 ± 2
4 min	210 ± 38	66 ± 14	87 ± 3	73 ± 3
10 min	177 ± 31	59 ± 10	89 ± 4	72 ± 2
SCh group ($n = 8$)				
Baseline	193 ± 23	92 ± 12	99 ± 4	76 ± 4
1 min	269 ± 41	126 ± 35	114 ± 6*	96 ± 6*
4 min	334 ± 48*	136 ± 31	108 ± 4	85 ± 4
10 min	210 ± 27	117 ± 35	92 ± 3	77 ± 5
Pretreatment group ($n = 7$)				
Baseline	149 ± 25	68 ± 14	95 ± 5	77 ± 6
1 min	157 ± 22	71 ± 17	94 ± 3	79 ± 5
4 min	156 ± 29	66 ± 19	96 ± 5	78 ± 6
10 min	165 ± 30	66 ± 18	84 ± 2	73 ± 6

Values are means ±SEM.
*Significantly different from control ($P < 0.05$).

of which were transient and observed at almost the same time in the SCh group, represented the initial agonistic action of SCh on the nicotinic receptors at both the neuromuscular junction (4) and the sympathetic ganglia (3). Nigrovic et al. also reported in their review that intravenous administration of SCh significantly increases plasma NE concentrations, and postulated that SCh might stimulate the nicotinic receptors on postganglionic sympathetic terminals, leading to explosive release of NE (6,7). Although the present study does not permit us to evaluate any possible interaction between SCh and alcuronium at the receptor level, it is highly possible that alcuronium, administered 5 min before SCh, combined with the nicotinic receptors both at the neuromuscular junction and the sympathetic ganglia prior to SCh and blocked the agonistic action of SCh on these receptors. If so, similar results would be expected when patients are pretreated with *d*-tubocurarine, which has a slightly greater blocking action than alcuronium on sympathetic ganglia, but not with pancuronium, vecuronium or atracurium, which are not known to have sympathetic ganglion blocking action (8).

The magnitude of increases in plasma NE concentrations and the absence of significant increases in plasma E concentrations after SCh during enflurane anesthesia in our SCh group were similar to the results obtained during halothane-nitrous oxide anesthesia (6), suggesting that there is no difference in catecholamine release by SCh in both anesthetic circumstances.

In summary, SCh-induced increases in plasma NE concentrations, systolic blood pressure and heart rate were significantly attenuated by prior administration of alcuronium.

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Antinociceptive Effects and Spinal Cord Tissue Concentrations after Intrathecal Injection of Guanfacine or Clonidine into Rats

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POST C, GORDH T Jr, MINOR BG, ARCHER T, FREEDMAN J. Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine into rats. Anesth Analg 1987;66: 317–24.

In the present study, the antinociceptive effects of intrathecal injections of the α_2-adrenoceptor agonists clonidine and guanfacine in rats was determined to establish their dose-response curves. Spinal cord tissue concentrations were also determined in a separate group of animals. Guanfacine was found to be more potent than clonidine and had a considerably longer duration of action. Thus, whereas the analgesic effect of clonidine declined to baseline by 4 hr after injecting doses of up to 50 μg, guanfacine still showed a considerable effect 18 hr after injecting both 25 and 50 μg. With both compounds, concentration gradients existed within the spinal cord. In the experiments with guanfacine, the region in the spinal cord tissue with the highest concentrations 10 min after injection contained around 30 pmol/mg wet weight. At 3 hr, this figure was around 20 pmol/mg. With clonidine, on the other hand, the concentration decreased from the maximal level of 200 pmol/mg at 10 min to 10 pmol/mg at 3 hr. On all occasions, except 10 min after injecting clonidine, it was found that the maximal tissue concentrations for both drugs remained below the cervical spinal cord, i.e., the rostral spread was less than expected, especially with drugs with such a long duration of action. The present investigation demonstrates analgesic effects of both clonidine and guanfacine after intrathecal administration, with guanfacine proving more potent and longer acting; the difference in duration of action is probably attributable to differences in rates of elimination of the drugs from spinal cord tissue.

Key Words: PHARMACOLOGY—guanfacine. SYMPATHETIC NERVOUS SYSTEM, α-ADRENOCEPTOR AGONIST—clonidine, guanfacine. SPINAL CORD—clonidine, guanfacine effects.

Pain relief from the epidural or intrathecal administration of opiates has become an accepted clinical procedure. In addition, reports have recently appeared that suggest that epidural or intrathecal α-adrenoceptor agonists may also be useful analgesic agents for the relief of pain. Spinal α-adrenoceptor agonists probably produce pain relief by activating segmentally located receptors in the descending noradrenergic systems (1,2). Thus, intrathecal noradrenergic agonists (3–8) have antinociceptive effects. Recently, it was demonstrated clinically that the relatively selective α_2-adrenoceptor agonist clonidine has analgesic effects (9–11). When injecting drugs into the intrathecal space, a number of factors affect penetration into the adjacent tissues, redistribution from the site of action, elimination to the systemic circulation, and thus the rate of onset and duration of action (for review see 12). For the opiate drugs, the pharmacokinetical aspects of intrathecal administration have been characterized fairly well, and the duration of analgesia in both animals and humans after injection of opioid drugs is inversely related to the lipophilic properties of the substances (13–16).

The present investigation was undertaken, first, to study the antinociceptive effects of the α_2-adrenoceptor agonists guanfacine and clonidine after intrathecal injection in rats, and, second, to quantify the relationships among antinociceptive effects, tissue distribution, and duration of action.

Materials and Methods

Animals

Male Sprague-Dawley rats weighing 280–300 g were used. They were kept in animal rooms thermostatically maintained at 20°C with artificial lightings for 12 hr/day from 06.00 to 18.00 hr and housed in groups

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of five rats per cage for 5–7 days before being operated upon.

Surgical Procedure

The animals were anesthetized by using an intraperitoneal injection of an aqueous solution containing chloral hydrate, 42.5 g/L; ethanol, 90 g/L; propylene glycol, 428 g/L; sodium pentobarbital, 9.75 g/L; and magnesium chloride, 21 g/L. A catheter was placed in the lumbar subarachnoid space, as described previously (17). In brief, a PE10 polyethylene catheter, stretched to double its length, was inserted into the spinal subarachnoid space via the cisterna magnum. At postmortem examination, it was found that the tip of the 8.5-cm catheter was in the Th13–L1 region. All animals included in the study had normal motor behavior and were allowed to recover for 5–7 days after operation before the drugs were injected intrathecally.

Injection Procedure

For the distribution experiments, guanfacine (Sandoz) and clonidine (Boehringer-Ingelheim) were injected in doses of 6 and 12.5 μg, respectively, dissolved in a volume of 10 μl 0.9% saline. ^{14}C-Guanfacine (synthesized at Astra Laboratories) and ^{3}H-clonidine (New England Nuclear) were added to the drug solutions in a quantity of 0.1 μCi for ^{14}C-guanfacine and 1.0 μCi for ^{3}H-clonidine. After the drug solutions were injected, 15 μl saline was injected to flush the catheters. For testing the antinociceptive effects, separate groups of animals were injected with clonidine and guanfacine at the doses indicated in Figures 1–4. Control rats were given 25 μl 0.9% saline. Different groups of animals were used for testing antinociceptive effects and spinal cord tissue concentrations of guanfacine and clonidine.

Nociceptive Testing

Before the nociceptive tests were performed, the animals were adapted to the test situations on three consecutive days by placing them on the plate to be used for hot plate testing while it was at room temperature and by putting them into the plastic restrainer used in the tail-flick test.

For the hot plate test (18), a heated aluminum surface, maintained thermostatically at 58°C, was used. The animals were confined to the plate by a Plexiglas container. The reaction defined as a nociceptive response was hind-paw lick or vigorous stepping or shaking of the hind legs. The reaction latency under baseline conditions was normally in the range of 4–5 sec. A cutoff time of 30 sec was used in the absence of a response.

The tail-flick test (19) was performed by directing a concentrated light beam at the tip of the tail at an intensity sufficient to produce heat. The time to onset of flicking of the tail was taken as latency. A cutoff time of 10 sec was used to avoid tissue damage.

Preparation of Tissue Samples

At the times indicated in Figures 5 and 6, separate groups of animals injected with radioactively labeled guanfacine or clonidine were anesthetized with pentobarbital (60 mg/kg, intraperitoneally). The spinal column was dissected free and the cord, exposed after bilateral laminectomy, carefully excised after cutting the spinal nerve roots. The tissue was then divided into 5-mm-long segments, each weighing 20–40 mg.

Measurement of Tissue Concentrations

Each segment was weighed and digested in 1.0 ml Soluene 350 (Packard Instruments) at 50°C. A volume of 10 ml toluene with Permablend (Packard Instruments) was added to a concentration of 5.5 g/L when the tissue was fully solubilized, and the radioactivity determined in a Packard 2430 liquid scintillation counter.

Thin Layer Chromatography

To ascertain that the radioactivity represented parent compounds and not metabolites, thin layer chromatography (TLC) was performed. Spinal cords were excised as described above from animals injected with 6 μg guanfacine and sacrificed 1 hr later. The cords were cut into small pieces and homogenized in 2 ml of water using a Sonifier cell disrupter equipped with a microtip. The homogenate was acidified (pH 1) with 1M HCl and extracted with chloroform 3 × 5 ml. The extraction procedure was repeated at pH 10. The organic phases were dried over anhydrous sodium sulfate, filtered, and evaporated under nitrogen to dryness. The residues were dissolved in 2 ml ethanol and aliquots measured for radioactivity content.

Some material remained undissolved in the ethanol. The solution was therefore transferred to new vials, evaporated to dryness, and the residue dissolved in 100 μl chloroform. This solution was then passed through a silica plug, which was eluted with chloroform and ethanol. The eluates containing radioactivity were analyzed by TLC. The samples from the extraction procedure were analyzed in a Packard Tri-Carb 460 liquid scintillation counter. Samples of the fractions containing radioactivity were applied on

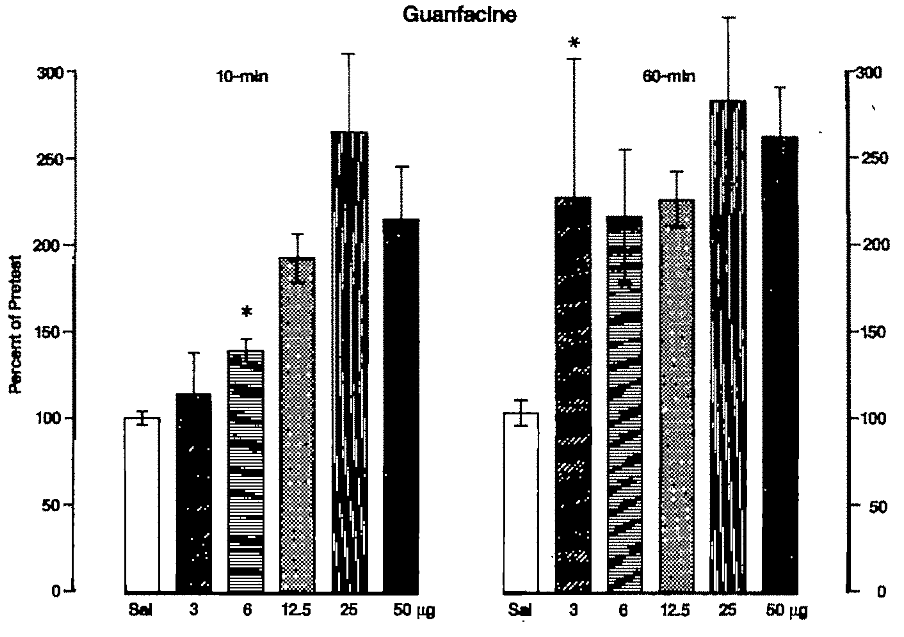

Figure 1. Antinociceptive effects of guanfacine after intrathecal administration of doses of 0, 3, 6, 12.5, 25, and 50 µg. The effects were determined 10 and 60 min after injection and are expressed as medians ± quartiles from four to six animals per group. Note an increased antinociceptive effect with 3 µg between 10 and 60 min. The differences between the saline (SAL) and guanfacine groups were statistically significant ($P < 0.02$; Mann-Whitney U-test) as indicated by asterisks with doses of 6 µg and above at 10 min and with doses of 3 µg and above at 60 min.

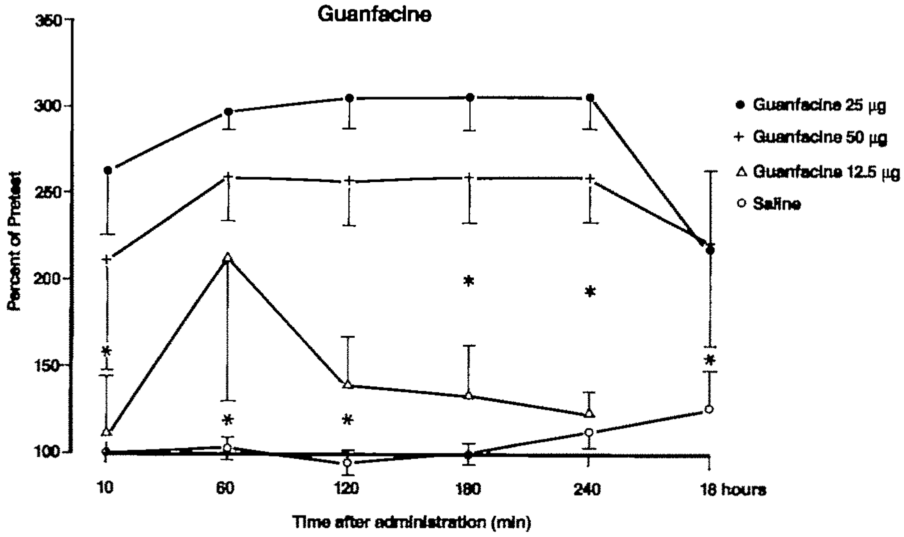

Figure 2. Time-response curves for antinociceptive effects after intrathecally administered guanfacine in doses of 0, 12.5, 25, and 50 µg. The results are expressed as medians ± quartiles from four to six animals per group, and statistical significance ($P < 0.02$; Mann-Whitney U-test) is indicated by asterisks. This experiment was performed in different animals than those used in Figure 1. The difference between saline and guanfacine was statistically significant for the 25 and 50 µg groups at 10, 180, and 240 min and 18 hours, and the 12.5 µg group was statistically significantly different from the saline group at 60 and 120 min.

Polygram SilG/UV254 5 × 20-cm plates (Macherey-Nagel) or Kieselgel 60F-254 10 × 20-cm plates (Merck). The plates were eluted in three solvent systems: 1) EtOAc/MeOH/H_2O (8/3/2); 2) $CHCl_3$/EtOH, NH_4OH (80/20, ten drops); 3) $CHCl_3$/CH_3COOH/CH_3OH (40/4/3). The plates were scanned for radioactivity in a Berthold automatic TLC linear analyzer connected to a microcomputer.

Statistical Calculations

Pairwise testing of statistically different antinociceptive effects and tissue concentrations between the saline and dose groups and time groups, respectively, was performed with the Mann-Whitney U-test (20). A value of $P < 0.02$ was considered statistically significant.

Results

Antinociceptive Effects

Acute intrathecal administration of neither clonidine nor guanfacine produced antinociceptive effects in the hot plate test. In the tail-flick test, guanfacine, at the 10-min interval, had a significant antinociceptive effect (as measured from the percent of pretest response latencies) as shown in comparison with the saline

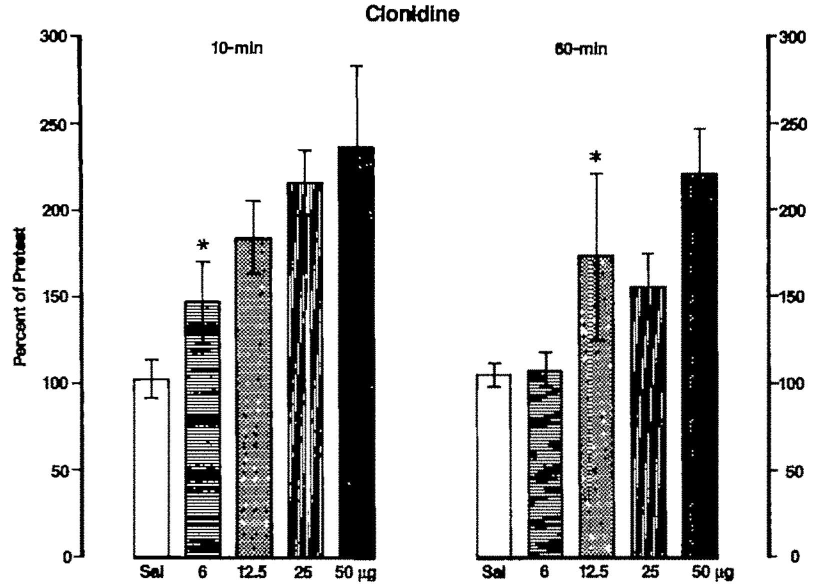

Figure 3. Antinociceptive effects of clonidine after intrathecal administration of doses at 0, 6, 12.5, 25, and 50 µg. The effects were determined 10 and 60 min after injection and are expressed as medians ± quartiles from four to six animals per group. The differences between saline (SAL) and clonidine were statistically significant ($P < 0.02$; Mann-Whitney U-test) as indicated by asterisks with doses of 6 µg clonidine and above at 10 min and with 12.5 µg and above at 60 min.

group in doses of 6 µg and above (Fig. 1). No gross motor or behavioral effects were observed. After 60 min, a significant antinociceptive effect was observed in doses of 3 µg and above (Fig. 1). Again, no motor or behavioral effects were observed.

The antinociceptive effects of the 25 µg and 50 µg doses of guanfacine were long acting (Fig. 2), significant antinociceptive effects still being present for 18 hr after administration. The apparently greater effect of the 25 µg dose as compared with the 50 µg dose of guanfacine was due in part to the fact that both doses had almost maximal effects, with a 10-sec latency, lasting up to 240 min, and in part to the fact that in the 50 µg group one rat had a faster reaction time than the others, all of which were nonresponders in the tail-flick test. The difference between the two groups was, furthermore, not statistically significant. The antinociceptive effects of the 12.5 µg dose were present at 180 min but not at 240 min.

With clonidine, a significant antinociceptive effect was present with doses of 6 µg and above whereas after 60 min a significant antinociceptive effect was seen only with doses of 12.5 µg and above (Fig. 3). Piloerection and sedation were obtained after doses of 25 µg and 50 µg. No motor effects were observed. The antinociceptive effects of the 12.5 µg and 50 µg doses were of similar duration, lasting up to 180 min (Fig. 4).

Spinal Cord Tissue Concentrations

When the tissue concentration of guanfacine was determined 10 min after injection of 6 µg, there was a concentration gradient over the spinal cord with the maximum concentration, 33 ± 5 (x̄ ± SEM) pmol/mg tissue, being four segments above the tip of the catheter. The most rostral five segments had a concentration of 14 ± 2 pmol/mg spinal cord, and the corresponding value for the most caudal five segments was 21 ± 2 pmol/mg (Fig. 5*A*). The concentration was slightly lower, but not statistically significant at 60

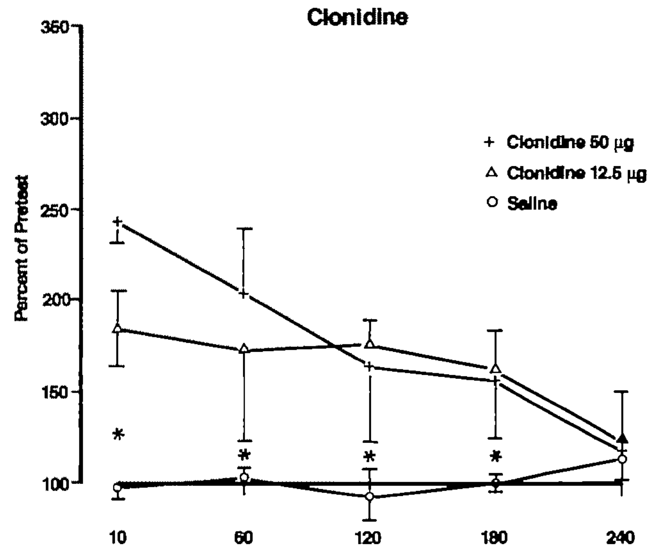

Figure 4. Time-response curves for antinociceptive effects after intrathecally administered clonidine in doses of 0, 12.5, and 50 µg. The results are expressed as medians ± quartiles from four to six animals per group, and statistical significance ($P < 0.02$; Mann-Whitney U-test) is indicated by asterisks. This experiment was performed in different animals than those used in Figure 3. The differences between saline and clonidine were statistically significant for both groups between 10 and 180 min, with no significant differences between the groups 240 min after injection.

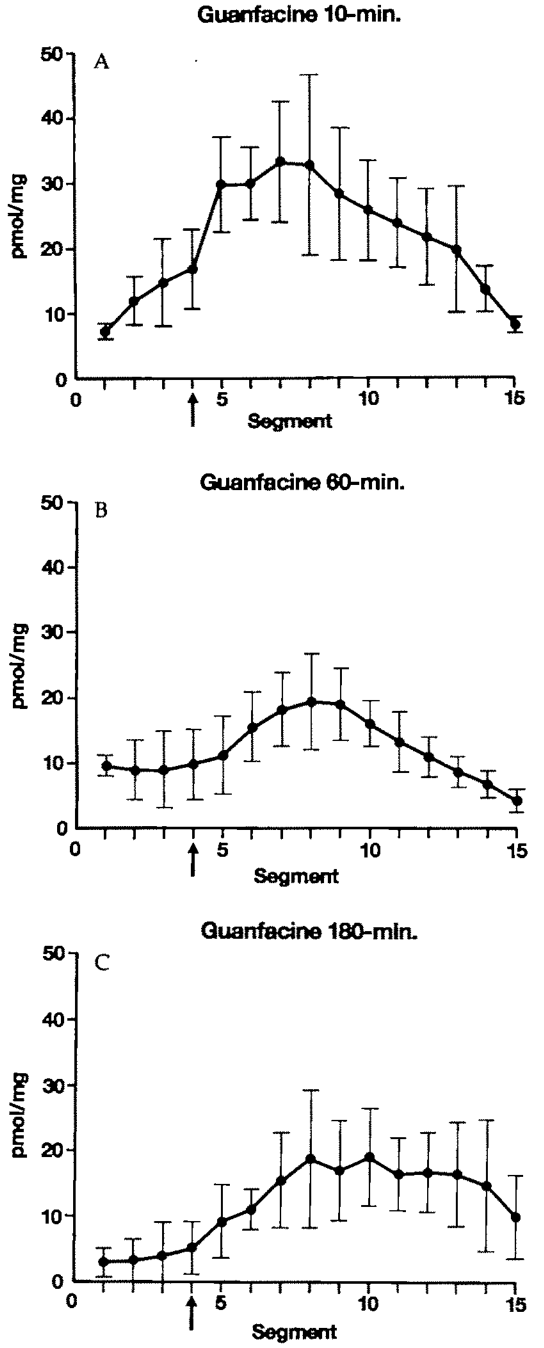

Figure 5. Spinal cord tissue concentration of guanfacine after injection of 6 μg radioactively labeled drug. The results are expressed as means ± SEM from four to six animals sacrificed at 10 (A), 60 (B), and 180 min (C) after drug administration. The tip of the catheter was at the lumbar enlargement as indicated by the arrow (the Th13–L1 region), and the most rostral spinal cord tissue, segment 15 in the figures, was taken from the cervical region (C1–C2). No statistically significant differences in segmental concentrations were found between 10 and 60 or between 60 and 180 mins.

min, the maximum being 19 ± 3 pmol/mg (Fig. 5*B*). At this time, the highest concentrations were still found four to five segments rostrally from the tip of the catheter. Maximal concentrations 3 hr after injection were similar and statistically not significantly different from those found at 1 hr (Fig. 5C). In animals sacrificed 4 hr after injection, the concentration was 6.6 ± 2.4 pmol/mg in the fourth segment above the tip of the catheter, and the most cervical segment of the cord had a concentration of 0.94 ± 0.92 pmol/mg (data not shown). The same pattern was found 8 hr after injection with a concentration of 5.9 ± 1.5 pmol/mg and 1.1 ± 0.5 pmol/mg in the fourth and most rostral segments, respectively. Sixteen hours after injection, radioactivity was present in the cord in the range of 500–1000 DPM in the tissue samples with the highest concentrations, which was equivalent to a concentration of 1.21 ± 0.23 pmol/mg four segments above the injection site and 0.31 ± 0.14 pmol/mg in the most rostral spinal cord specimen.

In the animals injected with clonidine and sacrificed 10 min after injection, there was a large variation in concentration, with a maximum level of 218 ± 78 pmol/mg tissue (Fig. 6*A*). With animals sacrificed 60 min after injection, the same profile was found as after guanfacine, with the highest concentration of 29 ± 5 pmol/mg in the second segment above the tip of the catheter (Fig. 6*B*). The decrease from 10 min to 1 hr was statistically significant in all segments except the most caudally located. At the time of the final measurement of tissue levels at 3 hr, the maximum concentration, around 10 pmol/mg, was still found four to five segments above the tip of the catheter (Fig. 6C); the most rostral segment at this time had a concentration of between 1 and 2 pmol/mg.

After injection of guanfacine, approximately 85% of the radioactivity was extractable from the tissue, and about equal amounts were found in the acidic and alkaline extracts. Only one TLC band containing radioactivity was found in the three systems, and it corresponded to the parent guanfacine.

Discussion

When injected intrathecally in the present study, both clonidine and guanfacine, as described elsewhere, produced antinociceptive effects (5,8,21) in rats as determined by the tail-flick test. Of the two compounds, guanfacine had a considerably longer duration of action than clonidine, and this finding was consistent with results showing that guanfacine was eliminated from the spinal cord tissue more slowly than clonidine.

In the study by Reddy et al. (5), clonidine at a dose

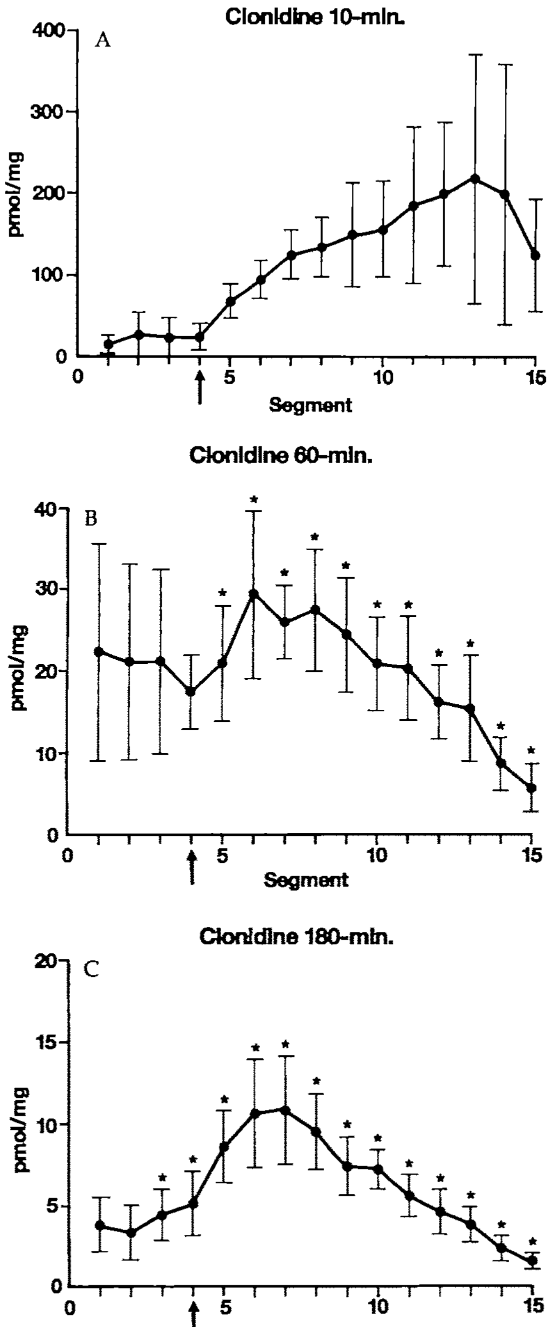

Figure 6. Spinal cord tissue concentration of clonidine after injection of 12.5 μg radioactively labeled drug. The results are expressed as means ± SEM from four to six animals sacrificed at 10 (A), 60 (B), and 180 min (C) after drug administration. The tip of the catheter was at the lumbar enlargement as indicated by the arrow (the Th13–L1 region), and the most rostral spinal cord tissue, segment 15 in the figures, was taken from the cervical region (C1–C2). The differences between 10 and 60 and between 60 and 180 min were statistically significant ($P < 0.02$; Mann-Whitney *U*-test) as indicated by asterisks.

Table 1. Physicochemical Properties of Guanfacine and Clonidine and Degree of Ionization at pH 7.4

Drug	pKa	log P[a]	% ionized[b]
Guanfacine	7.9	0.8	76
Clonidine	7.1	1.3	33

Data from References 33 and 34.

[a] Partition coefficient between *n*-octanol/buffer at pH 7.4. The higher the value, the greater is the amount of uptake by the lipophilic *n*-octanol.

[b] According to the Henderson-Hasselbalch equation, pKa = pH + $\log \frac{[BH^+]}{[B]}$, BH^+ being the ionized form.

of 400 nmol (110 μg) injected intrathecally in rats had a strong and long-acting antinociceptive effect in both the tail-flick and hot plate tests. The duration of action was substantially longer than for catecholamines. The same study also demonstrated that antinociceptive potency was similar in both the tail-flick and the hot plate tests, the threshold for antinociception being about 30 nmol. The same long duration was found in the monkey with 2 mg intrathecal clonidine using the shock-titration paradigm (8). In the present study, we found that latency in the tail-flick test was affected, whereas the hot plate latency was unchanged. Morphine, methionine-enkephalin, and norepinephrine also have similarly different effects in tail-flick and hot plate tests; the effect of norepinephrine is greater than that of opiates in terms of tail-pinch responses but not hot plate responses (22). In a recent study, we similarly found a greater antinociceptive response of morphine after intrathecal injections with the tail-flick test than with the hot plate test (16).

The mechanism of action responsible for the development of analgesia after intrathecal clonidine and guanfacine probably involves activation of spinally located α_2-adrenoceptors as the response to intrathecally administered noradrenergic agents is antagonized by selective antagonists to this receptor subtype (21, 23). This has also been demonstrated for a clonidine analogue, U-47,476A (24), and for intrathecally administered guanfacine (21). Guanfacine, as well as clonidine, is a selective agonist to the α_2-receptors (25), and receptor binding studies indicate that the selectivity for α_2- over α_1-receptors is greater with guanfacine than with clonidine (26–28), the binding of guanfacine being predominantly to the high affinity state of the α_2-adrenoceptor (29).

In the spinal cord, both α_1- and α_2-adrenoceptor binding has been demonstrated by autoradiography using specific ligands to the receptor subtypes (29). Thus, para-aminoclonidine binding occurs predominantly in the dorsal horn region, with high binding to the substantia gelatinosa and to the intermediolateral cell column (30–31). Localization of the binding in the primary pain afferent terminal region of the spinal cord supports the notion that α_2-adrenoceptors have a function in pain modulation. The localization of binding to the intermediolateral cell column (30) provides evidence that the effects on sympathetic nervous activity by local injection of clonidine into the intermediolateral cell column (32) are attributable to a spinal site of action.

The present findings offer evidence to suggest a longer duration of antinociceptive action by guanfacine than clonidine. The physicochemical properties of the two compounds are, in terms of pKa and log P values, quite similar (Table 1) (33,34). Calculations using the Henderson-Hasselbalch equation show that at pH 7.4, guanfacine, a stronger base, is 76% ionized, whereas only 33% of clonidine is ionized (Table 1). This, together with the larger log P value for clonidine (Table 1), probably explains, at least in part, the longer duration of action of guanfacine as compared with clonidine. Both the higher degree of ionization and the lower log P of guanfacine make this compound less prone to diffusion out of the subarachnoid space into the circulation than clonidine. For opioids, the same inverse relationship exists between lipophilicity and duration of analgesia (35,16).

The rates of elimination of clonidine and guanfacine could also be influenced by effects on local blood flow if the blood vessels have the receptors activated by the drugs. An extensive sympathetic innervation of spinal cord vessels has been demonstrated (36). Therefore, the local administration of agents with an effect on the sympathetic tone might have an effect on the spinal microcirculation. Phenylephrine reduces the spinal cord blood flow in a dose-dependent manner (37), and the selective α_2-adrenoceptor agonists clonidine (38) and guanfacine (Post et al., unpublished results) have similar but weaker effects. With guanfacine, a dose of 25 μg is required to produce a small but statistically significant decrease in the blood flow, whereas the present investigation demonstrates an analgesic effect at much lower doses. When comparing the two compounds, it seems unlikely that differences in potency and duration of action represent different effects on local blood flow. To exclude this possibility fully, however, more experiments are required that address this issue specifically.

The tissue concentration gradients in the present study demonstrate that not only did clonidine have a high initial concentration but that this also was reached in the most rostral segments of the cord. This could explain the fact that clonidine but not guanfacine produced supraspinal side effects with sedation after the higher doses (25 and 50 μg). Another side effect that might occur to an extent dependent on the degree of rostral redistribution is sympathetic blockade with a spinal site of action in the thoracic region. This issue was not addressed in the present investigation, but was previously investigated (39,40).

In conclusion, guanfacine and clonidine produce analgesia after intrathecal injection in rats, and the considerably longer duration of action for guanfacine is reflected by a slower elimination from the spinal cord tissue. It is, therefore, possible that guanfacine might prove to be a better drug than clonidine for pain treatment with intrathecal or epidural administration because of its longer duration of action.

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Lidocaine Modifies the Effect of Succinylcholine on Muscle Oxygen Consumption in Dogs

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The effects of succinylcholine (SCh: 2 mg/kg) alone and in combination with lidocaine (4.5 mg/kg in two increments) on muscle oxygen consumption ($\dot{V}O_2$) and blood flow (MBF) in normal and denervated gastrocnemius muscle were studied in 18 dogs anesthetized with halothane (0.94%, end tidal) to examine the interactions of both drugs at the neuromuscular junction. In an additional five dogs with normal gastrocnemius muscle, the effects of lidocaine alone on $\dot{V}O_2$ and MBF were also studied. In normal muscle, $\dot{V}O_2$ increased as much as 150% with SCh alone, while with the combination of lidocaine and SCh, $\dot{V}O_2$ remained unchanged. MBF remained unchanged with SCh alone and the combined use of lidocaine and SCh. Neither the $\dot{V}O_2$ nor MBF was affected by lidocaine alone. In denervated muscle, $\dot{V}O_2$ increased as much as 304% with SCh alone and MBF increased 115%. With the combined use of SCh and lidocaine the $\dot{V}O_2$ in denervated muscle increased up to 360% with a 290% increase in MBF. These findings indicate different effects of lidocaine on metabolic and circulatory responses to SCh in normal and in denervated muscles in dogs.

Key Words: ANESTHETICS, LOCAL—lidocaine. NEUROMUSCULAR RELAXANTS—succinylcholine. MUSCLE—oxygen consumption.

Succinylcholine (SCh) increases muscle oxygen consumption ($\dot{V}O_2$). This is primarily the result of SCh-induced skeletal muscle contractions (fasciculations) (1). The muscle contractions, and hence the increase in muscle $\dot{V}O_2$ with SCh, can be prevented or attenuated by pretreatment with subparalyzing doses of nondepolarizing muscle relaxants, probably because of competitive interaction of the drugs at neuromuscular junctions (1). Lidocaine also prevents SCh-induced muscle contractions (2). However, unlike pretreatment with nondepolarizing muscle relaxants, lidocaine augments SCh-induced muscle relaxation (3). The effect of pretreatment with nondepolarizing muscle relaxants on SCh-induced changes in $\dot{V}O_2$ has been well documented in both normal and denervated muscles (1,4), but the effect of lidocaine remains unclear. The present study, designed to examine the effect of lidocaine on SCh-induced increases in $\dot{V}O_2$, found a difference in response in normal and denervated muscles.

Methods

Twenty-three unpremedicated mongrel dogs weighing 9.0–19.5 kg were anesthetized with thiamylal (15–30 mg/kg) intravenously. Endotracheal anesthesia was maintained with halothane in 50% oxygen in nitrogen. Ventilation was adjusted to maintain Pa_{CO_2} at 33 ± 1 mm Hg and Pa_{O_2} at 250 ± 10 mm Hg with a Harvard pump. The concentration of end-tidal halothane measured by gas chromatography (Shimadzu 4A-PTF, Kyoto, Japan) was kept at 0.94 ± 0.04% throughout the study. Catheters were placed in the femoral artery for pressure measurement and blood sampling and in the external jugular vein for infusion of fluid and drugs. Heparin was administered intravenously (2000 U/hr). The gastrocnemius muscle was isolated and all the veins draining from the muscles other than the gastrocnemius were ligated as described by Stainsby and associates (5). Muscle blood flow (MBF) in the gastrocnemius was measured using an electromagnetic flow meter detector (Nihon Koden Kogyo, Tokyo, Japan; internal diameter 3 mm). The detector was placed in the femoral vein proximal to the last branch draining the muscle and the drained blood was returned to the femoral vein.

To ensure the accuracy of the measurements, the

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flow meter included a nonocclusive zero and a 3-sec time constant. In addition, it was frequently calibrated by direct timed measurements of gastrocnemius MBF. The $\dot{V}O_2$ of gastrocnemius muscle was calculated as the product of MBF and the oxygen content differences between arterial and muscle venous blood and expressed in terms of wet weight of the muscle as removed at necropsy. Arterial and venous oxygen contents were calculated from measurements of oxyhemoglobin (IL182 CO-oximeter) and oxygen tension (IL 313 electrode).

The dogs were divided into five groups. In group 1, five dogs with normal muscles were given SCh (2 mg/kg) alone. In group 2, five dogs with normal muscle were given lidocaine (4.5 mg/kg in two increments) and SCh (2 mg/kg). In group 3, five dogs with normal muscle were given lidocaine (4.5 mg/kg in two increments) alone. In group 4, four dogs with denervated muscle were given SCh (2 mg/kg) alone. In group 5, four dogs with denervated muscle received lidocaine (4.5 mg/kg in two increments) and SCh (2 mg/kg). In all dogs given lidocaine, 3 mg/kg was administered 5 min before and then additional 1.5 mg/kg was given 5 min after SCh. In group 3, saline was administered instead of SCh. In the denervated muscle groups (groups 4 and 5), unilateral sciatic nerve section was performed under thiamylal (15–20 mg/kg) given intravenously 18–35 days beforehand. In all dogs, blood samples for measurements of pH, P_{O_2}, P_{CO_2}, hemoglobin, and saturation were obtained before and 3, 5, 7, 10, 15, and 30 min after SCh or saline administration. Plasma lidocaine concentrations in arterial blood in group 2 were measured by gas chromatography as previously described (6).

Changes within and between groups were tested for statistical significance using two-way analysis of variance followed by the least significant difference (LSD) test for multiple comparisons. Statistical significance was assumed with P values < 0.05.

Results

The results in dogs with normal muscles are summarized in Table 1. In group 1, SCh increased $\dot{V}O_2$ for 15 min, the maximum increase being 1.62 ml·min^{-1}·100 g^{-1} (150%) at 10 min. MBF was not changed by SCh. In group 2, the combination of lidocaine and SCh did not increase $\dot{V}O_2$—which, after SCh administration, was significantly less in group 2 than in group 1 at 5, 7, 10, and 15 min. MBF was not altered by the combined use of lidocaine and SCh. In group 3, neither $\dot{V}O_2$ nor MBF was affected by lidocaine alone.

The results in dogs with denervated muscles are summarized in Table 2. In group 4, SCh increased $\dot{V}O_2$ for 15 min and MBF for 10 min. The maximum increases in $\dot{V}O_2$ and MBF were 4.49 (304%) and 40.8 ml·min^{-1}·100 g^{-1} (115%), respectively, at 7 min. In group 5, the combined use of lidocaine and SCh increased $\dot{V}O_2$ and MBF for 15 min. The maximum increases in $\dot{V}O_2$ and MBF were 6.18 (360%) and 84.1 ml·min^{-1}·100 g^{-1} (290%), respectively. The increase in $\dot{V}O_2$ by SCh was significantly greater in group 5 than in group 4 at 5 and 7 min. Thus, the increases in $\dot{V}O_2$ and MBF were not attenuated by lidocaine but instead were increased.

Plasma lidocaine concentrations in arterial blood for 15 min in group 2 ranged from 2.1 to 6.6 μg/ml.

Discussion

The present study demonstrates that lidocaine attenuates the SCh-induced increase in $\dot{V}O_2$ in normal muscle but augments it in denervated muscle. Gronert and associates (4) reported that 0.25 mg/kg SCh doubles $\dot{V}O_2$ in normal muscle and quadruples $\dot{V}O_2$ in denervated muscle. Our results are in agreement with their results. Why pretreatment with lidocaine attenuates the increase in $\dot{V}O_2$ due to SCh in normal muscle may be related to events taking place at pre- and postjunctional sites (7). The prejunctional release of acetylcholine associated with SCh (8), for example, is attenuated by lidocaine enough to decrease muscle contractions produced by SCh (9) and, thus, decreases the SCh-induced increase in muscle $\dot{V}O_2$. Release of acetylcholine from the nerve terminal by electrical stimulation is also reduced by lidocaine in concentrations in the range of those used in the present study (10^{-5} M) (10). If the effect of lidocaine on the electrically induced presynaptic release of acetylcholine also applies to SCh-mediated release of acetylcholine as seen in the present study, the effect of lidocaine may be attributable at least in part to its prejunctional effects. The absence of effects of lidocaine alone on $\dot{V}O_2$ suggests that the decrease in acetylcholine at nerve terminals with lidocaine, if present, did not reach a level that causes a decrease in $\dot{V}O_2$ in normal resting muscle because of the endplates' large safety factor in normal muscle.

The mechanism for the SCh-induced increases in $\dot{V}O_2$ in normal muscle also involves depolarization by SCh of postjunctional muscle membranes with the generation of action potentials and muscle contractions (fasciculations) (1). Lidocaine is an open channel blocker that plugs Na^+ channels "use-dependently" at the end plate and may desensitize the acetylcholine receptor to agonists (11) (as may be the case in the presence of SCh), and/or produces a nondepolarizing

Table 1. Modification of Muscle Oxygen Consumption ($\dot{V}O_2$) and Blood Flow (MBF) by Lidocaine after Succinylcholine (SCh) Administration in Normal Muscle

		Baseline	After SCh administration (min)					
			3	5	7	10	15	30
Group 1 (SCh alone)	$\dot{V}O_2$	1.12 ± 0.25	1.92 ± 0.45^a	2.49 ± 0.65^{b,c}	2.71 ± 0.72^{b,c}	2.74 ± 0.66^{b,d}	2.48 ± 0.57^{b,c}	1.60 ± 0.35
	MBF	34.1 ± 7.1	31.7 ± 7.7	34.7 ± 6.5	34.9 ± 6.6	35.2 ± 6.0	34.7 ± 4.6	34.4 ± 5.4
Group 2 (lidocaine + SCh)	$\dot{V}O_2$	1.37 ± 0.31	1.82 ± 0.32	1.84 ± 0.32^c	1.94 ± 0.22^c	1.83 ± 0.30^d	1.65 ± 0.40^c	1.35 ± 0.26
	MBF	31.7 ± 7.1	31.9 ± 5.7	31.5 ± 4.6	30.4 ± 4.3	28.0 ± 5.6	26.9 ± 6.6	26.1 ± 5.5
Lidocaine concentration (μg/ml)			2.8 ± 0.6	2.1 ± 0.3	6.6 ± 1.1	3.7 ± 0.5	2.4 ± 0.3	1.5 ± 0.1
Group 3 (lidocaine alone)	$\dot{V}O_2$	1.16 ± 0.28	1.09 ± 0.24	1.24 ± 0.30	1.24 ± 0.34	1.34 ± 0.47	1.50 ± 0.59	1.14 ± 0.26
	MBF	31.2 ± 6.0	25.8 ± 3.1	27.4 ± 3.5	25.1 ± 4.3	23.1 ± 6.6	27.0 ± 6.8	32.7 ± 9.5

Values are means ± SEM. Units: $\dot{V}O_2$, MBF; ml·min^{-1}·100 g^{-1}. $n = 5$ in each group.
[a] $P < 0.05$ when compared with control.
[b] $P < 0.01$ when compared with control.
[c] $P < 0.05$ when groups 1 and 2 were compared at the same time period.
[d] $P < 0.01$ when groups 1 and 2 were compared at the same time period.

Table 2. Modification of Muscle Oxygen Consumption ($\dot{V}O_2$) and Blood Flow (MBF) by Lidocaine after SCh Administration in Denervated Muscle

		Baseline	After SCh administration (min)					
			3		7	10	15	30
Group 4 (SCh alone)	$\dot{V}O_2$	1.50 ± 0.13	5.34 ± 0.77^b	5.86 ± 0.66^{b,c}	5.99 ± 0.62^{b,c}	5.50 ± 0.86^b	4.69 ± 0.83^b	2.75 ± 0.27
	MBF	38.9 ± 6.1	72.8 ± 11.8^a	78.2 ± 9.6^a	79.7 ± 7.0^{a,c}	76.2 ± 6.9^a	68.9 ± 4.0	47.2 ± 4.6
Group 5 (lidocaine + SCh)	$\dot{V}O_2$	1.77 ± 0.17	6.46 ± 0.53^b	7.85 ± 0.17^{b,c}	7.95 ± 0.75^{b,c}	6.71 ± 0.81^b	5.38 ± 0.62^b	1.89 ± 0.10
	MBF	29.2 ± 2.6	83.9 ± 9.1^b	103.5 ± 10.4^b	113.3 ± 18.2^{b,c}	108.7 ± 22.4^b	94.8 ± 21.2^b	37.5 ± 6.0

Values are means ± SEM. Units: $\dot{V}O_2$, MBF; ml·min^{-1}·100 g^{-1}. $n = 4$ in each group.
[a] $P < 0.05$ when compared with control.
[b] $P < 0.01$ when compared with control.
[c] $P < 0.05$ when group 4 and 5 were compared at the same time period.

type of block (7). Thus, the postjunctional effects of lidocaine, including desensitization of receptors and nondepolarizing block, may be operative at the presence of SCh and hence decreased $\dot{V}O_2$.

In contrast to normal muscle, denervated muscles develop a persistent contracture after SCh. It is known that an increase in extrajunctional acetylcholine receptors contributes to the actions of SCh in denervated muscle (11). The striking SCh-induced increase in $\dot{V}O_2$ in denervated muscles in the present study probably reflects this supersensitivity phenomenon. The increase in $\dot{V}O_2$ was greater in the group given lidocaine than it was in the absence of lidocaine. This might be so because the prejunctional action of lidocaine, which reduces acetylcholine release by SCh, is not operative in denervated muscle. Alternatively, perhaps the increase in the sensitivity of denervated muscle to SCh cannot be counteracted by a desensitization or nondepolarizing action of lidocaine at the post- and extrajunctional levels. An explanation for the significant augmentation of SCh-induced increase in $\dot{V}O_2$ with the combined use of lidocaine in denervated muscle awaits further studies, including calcium ion dynamics at the cellular level in both normal and denervated muscles (12).

Blood flow in skeletal muscle is regulated by neurogenic, humoral, and metabolic factors (13). A close correlation between the increase in blood flow and the increase in oxygen consumption has been described in contracting muscle (14). However, our results show that MBF remained unchanged despite the increase in $\dot{V}O_2$ in normal muscle after SCh. Gronert et al. (4) reported results similar to ours. In denervated muscle, however, an increase in $\dot{V}O_2$ was accompanied by a striking increase in MBF in both studies. This appears to indicate that there may be a threshold value of $\dot{V}O_2$ beyond which further increases in $\dot{V}O_2$ increase MBF.

In summary, the present study demonstrates differential effects of lidocaine on muscular responses to SCh in normal and in denervated muscle, and suggests that lidocaine should be included among agents that modify the supersensitivity phenomenon produced by SCh in denervated muscle.

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Priming with Atracurium

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Priming with atracurium was evaluated by dividing 39 patients into 2 groups. All received 0.2 mg IV glycopyrrolate and fentanyl, 50 μg IV. Group 1 received saline, group 2 received 0.06 mg/kg atracurium and a stop watch was started. After 3.5 min the patients were asked to lift their heads and maximum negative inspiratory pressure (MIP) was measured. Anesthesia then commenced with thiopental and a twitch monitor was applied to the ulnar nerve. At 5 min group 1 received 0.36 mg/kg atracurium and group 2 was given 0.30 mg/kg atracurium. At 6.5 min intubation was accomplished in all but one patient in group 1 and all but one in group 2. Mean T_4/T_1 ratios at 90 sec were 0.73 in group 1 and 0.51 in group 2. This difference was statistically significant ($P < 0.001$). Bucking on the endotracheal tube occurred in 72% of patients in group 1 and 62% of those in group 2 (not significant). Intubating conditions were "excellent" in 56% of those in group 1 and 75% in group 2 (not significant). "Good" conditions were seen in 33% of group 1 and 15% of group 2 patients (not significant). "Fair" conditions were noted in 6% of patients in group 1 and 5% of group 2 patients (not significant). The time to maximum twitch depression was 11.3 min and 11.5 min in groups 1 and 2 respectively (not significant). All patients in group 1 could sustain head lift whereas four patients in group 2 could not (not significant). A decrease in MIP was noted in 38% of patients in group 2, but MIP was not decreased in those in group 1. This difference was statistically significant ($P < 0.005$). We conclude that priming with atracurium, although providing a small improvement in T_4/T_1 ratio at intubation, does not significantly improve intubating conditions. It is complex, time consuming, is not well tolerated, and may put patients at risk for aspiration.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium.

A divided dose technique for facilitating rapid tracheal intubation with nondepolarizing relaxants was proposed by Foldes in 1984 (1). This method, known as the priming principle, consists of the administration of a small dose of a nondepolarizing muscle relaxant prior to induction of anesthesia, allowing sufficient time for the relaxant to reach myoneural junction receptors, then administering a second, larger dose to facilitate intubation. A suitable priming dose should allow the patient to maintain adequate respirations and to protect his airway while still awake. In situations where succinylcholine is contraindicated (2,3) this technique, if confirmed, would be a major advance.

Although recent papers (4–7) evaluated the use of the priming principle with atracurium, no previous study evaluating the priming principle with atracurium in awake patients has been undertaken. Such an evaluation is necessary to confirm the safety of a priming dose in patients at risk for pulmonary aspiration where a "rapid sequence" induction is necessary.

Methods and Materials

Thirty-nine adult ASA classification 1 and 2 patients free of neuromuscular diseases and on no medications affecting their sensitivity to nondepolarizing neuromuscular relaxants took part in this investigation after approval by our Institutional Review Board. All patients with anatomical conditions that would make endotracheal intubation difficult were excluded. All were given 0.2 mg IV glycopyrrolate and 50 μg fentanyl when the intravenous was started. In a randomized double blind manner, the patients were assigned to one of the following treatment sequences while awake: group 1 ($n = 18$), saline; group 2 ($n = 21$), 0.060 mg/kg atracurium. A stop watch was started. The volumes of the solutions administered were the same in both groups. After 3.5 min patients were asked to lift their heads for 5 sec and maximum in-

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Table 1. Maximum Inspiratory Pressure, Head Lift, Percent Intubated, Bucking, T_4/T_1, and Time to Onset of Maximum Relaxation

	Group 1	Group 2	P
Number	18	21	—
MIP change[b]	0%	−38%	<0.005
Head Lift, 5 sec[b]	100%	81%	[a]
Successful intubation at 6.5 min	94%	95%	[a]
Bucking	72%	62%	[a]
T_4/T_1 at 6.5 min[c]	0.73 ± 0.14	0.51 ± 0.23	<0.001
Time to maximal blockade (min)[c]	11.3 ± 3.1	11.5 ± 3.1	[a]

[a] Not a statistically significant difference.
[b] After priming dose or saline.
[c] Values are mean ± SD.

spiratory pressure (MIP) was measured to ensure that the patients could adequately protect their airways (8). Subjective complaints were noted. Thiopental was then administered in amounts sufficient to establish controlled ventilation with oxygen and nitrous oxide by mask at 4 min. At 5 min group 1 patients received 0.360 mg/kg atracurium and group 2 patients received 0.300 mg/kg atracurium. Here again equal volumes were administered.

After the administration of the thiopental, a DigiStim II nerve stimulator (Neuro Technology, Inc., Houston, TX) was used for train of four stimulation of the ulnar nerve with supramaximal impulses of 0.2 msec duration at 2 Hz through subcutaneous needles. The resulting thumb twitch was measured by a Grass FTO3C displacement transducer and recorded on paper with a Grass Polygraph. At 6.5 min, intubation of the trachea was attempted by an experienced laryngoscopist. Conditions for intubation were graded on the following scale: 4, excellent—easy and no reaction; 3, good—vocal cord movement present, jaw incompletely relaxed; 3, fair—vocal cord movement and moderate reaction; 1, impossible—just that: impossible. The T_4/T_1 ratio was recorded at 6.5 min, as was the time of maximal neuromuscular blockade. Twitch tension was within the range of the transducer used under these circumstances (9). Bucking or any movement in response to the intubation was also recorded by an investigator not involved in the laryngoscopy. Analysis of variance and Fischer's exact probability test were performed to detect any significant differences in dependent variables between the groups. A $P < 0.05$ was considered to represent statistical significance. All results are expressed as means ± SD.

Results

The results are summarized in Tables 1 and 2. There were no significant differences between the groups in terms of age, weight, or sex. All patients in group 1 could sustain 5 sec head lifts before induction. In group 2, 19% could not sustain head lift. This difference did not achieve statistical significance. Thirty-eight percent of patients in group 2 had reductions in MIP. No such changes were noted in group 1. This was statistically significant ($P < 0.005$).

Ninety-four percent of patients in group 1 were successfully intubated at 6.5 min, as were 95% of patients in group 2 (not significant). Intubating conditions are summarized in Table 2. Intubating conditions were excellent in 56% of group 1 patients and in 75% of those in group 2 (not significant). Conditions were considered good in 33% of those in group 1 and in 15% of those in group 2. In 6% of patients in group 1 and in 5% of group 2 patients conditions were fair (not significant). Bucking occurred in 72% of the group 1 patients and 62% of group 2 patients (not significant).

At 6.5 min mean train of four ratios were 0.73 in group 1 and 0.51 in group 2. This difference was statistically significant ($P < 0.001$). The time to maximum relaxation was 11.3 min in group 1 and 11.5 min in group 2 (not significant).

Although no patients in group 2 had severe adverse reactions while awake, most patients had severe ptosis and difficulty in swallowing shortly after the priming dose and many patients found the experience unpleasant and required much reassurance.

Discussion

Atracurium is a nondepolarizing muscle relaxant with a duration of action between succinylcholine and pancuronium (10) at usual doses. Attempts to use atracurium in place of succinylcholine for tracheal intubation have shown that even at doses of 0.6 mg/kg, the time to reach 100% neuromuscular blockade is nearly twice as long as it is with 1.0 mg/kg succinylcholine (11). Anesthesiologists have long known that

Table 2. Intubating Conditions

Group	Excellent	Good	Fair	Impossible
1	56%	33%	6%	6%
2	75%	15%	5%	5%

There were no significant differences between the two groups.

small doses of nondepolarizing muscle relaxants used to prevent fasciculations associated with succinylcholine are generally tolerated by awake patients, although occasional adverse reactions have been reported (12,13). Paton and Waud (14) have shown that 70% or more of the receptors at the neuromuscular junction must be occupied before single twitch depression occurs, although tetanic fade occurs at lower levels of receptor occupancy. In an attempt to speed the onset of atracurium, the concept of the priming principle has been suggested (15).

In a pilot study, we attempted to determine the maximum priming dose of atracurium that would be tolerated by awake, unpremedicated patients as determined by ability to sustain 5-sec head lift. Foldes had recommended 75–100 μg/kg. We found that 36% of patients given 0.070 mg/kg atracurium could not sustain head lift. This is hardly surprising because this dose represents the ED_{15} of atracurium (15). Brand et al. (8) have demonstrated the importance of head lift and inspiratory pressure in assessing recovery from muscle relaxants. Viby-Mogensen et al. (16), Lennmarken and Löfström (17), and others (18) have stressed the usefulness of head lift as a sign that patients can be extubated and left with little supervision. The present study shows that the incidence of inability to sustain 5-sec head lift could be reduced to 19% by reducing the dose of atracurium to 0.060 mg/kg. However, at this dose, 38% of our patients showed decreases in MIP as compared to their prepriming values.

Mirakhur et al. (19) have shown that intubating conditions 90 sec after 0.4 mg/kg atracurium are far from ideal. This is consistent with other investigators' reports (4,5,20). We felt that with a total dose of 0.360 mg/kg atracurium, any improvement in intubating conditions at 90 sec conferred by the priming principle over a single dose technique would be clearly seen.

Our results using 0.060 mg/kg atracurium given 5 min before 0.300 mg/kg demonstrate no significant improvement in intubating conditions, in the incidence of bucking on intubation, or the time to maximum twitch depression when compared to a bolus of 0.36 mg/kg atracurium, although there was a small improvement in T_4/T_1 at 6.5 min. Although it is not statistically significant, the fact that 19% of the patients given a priming dose of atracurium were unable to maintain 5-sec head lift is important in the clinical evaluation of this technique. This is especially so when it is noted that 38% of the patients in the priming group had reduced MIP after the priming dose, a result which did achieve statistical significance.

Geris et al. (4) in a non-double blind study in which 0.06 mg/kg atracurium was given to patients immediately before induction, with an intubating dose of 0.34 mg/kg given 3 min later, found no difference in intubating conditions at 2.5 min or the time to maximum twitch suppression. Their observation that 0.08 mg/kg atracurium given 3 min before 0.42 mg/kg resulted in acceleration of the times to intubation and maximum twitch suppression is not clinically relevant in a rapid sequence induction because our results suggest that such a large priming dose is not suitable for awake patients.

Nagashima et al. (5) studied 0.075 mg/kg atracurium given to anesthetized patients 6 min prior to 0.250 mg/kg. Our results again show that this priming dose is too large for awake patients.

Ramsey et al. (6) studied 0.050 mg/kg atracurium given to anesthetized patients 4.4 min prior to 0.350 mg/kg. Although intubating conditions were not evaluated, time to maximum relaxation, degree of block at 90 sec, and time to 25% recovery were not statistically different from a control group given 0.400 mg/kg as a bolus.

Weinberg et al. (7) studied 0.15 mg/kg atracurium given either as a bolus or as a 0.05 mg/kg dose given to anesthetized patients 5 min before 0.10 mg/kg. They showed a slightly more rapid onset of initial twitch depression in the divided dose group but there were no significant differences in time to maximum blockade between the groups.

In summary, this study shows that the priming principle with atracurium produces no improvement in intubating conditions when compared to a single bolus technique.

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Aminophylline Reversal of Flunitrazepam Sedation

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Seventeen otherwise healthy patients were given either intravenous physiologic saline, 5 ml, or aminophylline, 2 mg/kg, randomly 30 min after they were given intravenous flunitrazepam in doses adequate to produce sleep and sedation during spinal anesthesia for anorectal surgery. In the control group, mean sedation scores were 1.8 ± 0.3 and 1.0 ± 0.4 15 and 45 min after injection of placebo. Fifteen and 45 min after the injection of aminophylline the mean scores of sedation were 0.4 ± 0.2 and 0.2 ± 0.2, respectively. Even though the patients in both groups appeared to be equally alert and responsive after 75 min, Trieger tests revealed that psychomotor function was still significantly impaired in the control group 90 min after the injection of placebo. The amnesic effects of flunitrazepam were not affected by aminophylline. Aminophylline may be used to reverse the sedative and psychomotor effects of flunitrazepam.

Key Words: HYPNOTICS, BENZODIAZEPINES—flunitrazepam. ANTAGONISTS—aminophylline.

Flunitrazepam, a potent and long-acting benzodiazepine, is useful when given as an adjunct to local anesthesia (1). Its long duration of action is an advantage in patients scheduled for prolonged and extensive operative procedures. However, this may not be advantageous in patients undergoing short operations.

Various drugs have been suggested to reverse the soporific effects of benzodiazepines. Aminophylline reportedly reverses the sedative effects of flurazepam (2), diazepam (3), and lorazepam (4). With this background, we studied the effects of aminophylline on the sedative, psychomotor, and amnesic properties of flunitrazepam under controlled conditions in healthy adults.

Materials and Methods

Subjects

Seventeen healthy patients scheduled for anorectal surgery under spinal anesthesia were studied. None had a history of drug abuse and none received sedative or narcotic drugs for medication during the last month. Morphometric data are summarized in Table 1. Informed consent was obtained from each patient after a detailed explanation of the purpose of the study was given during the preoperative visit.

Protocol

Before the operation patients were given neither atropine nor any other drugs that would modify the effects of flunitrazepam. Baseline blood pressure (by sphygmomanometry) and heart rate (ECG) were recorded and a baseline Trieger (5) test was administered before the induction of spinal anesthesia. An intravenous cannula (18 gauge) was inserted and an infusion of Ringer's lactate was started when the patient arrived in the operating room. With the patient in the lateral position, lumbar puncture was performed using a 22-gauge spinal needle at the L4-5 intervertebral space. Once a free flow of cerebrospinal fluid was obtained, 5 ml of 2% prilocaine was injected intrathecally. The spinal needle was then withdrawn and the patient placed in the supine position with a 30° head up tilt. After a period of 5 min had elapsed, during which the blood pressure stabilized, patients were given 2 ml flunitrazepam (0.4 mg/ml) followed by increments (1 ml) until the eyelid reflex was abolished. The operation started within 5 min. About 30 min after the injection of flunitrazepam, which was when most surgical procedures were either completed or close to completion (Table 1), patients were given either 5 ml of 0.9% saline (group A, $n = 8$) or 2 mg/kg aminophylline (group B, $n = 9$) intravenously in a randomized fashion (random number tables) over 4 min.

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Table 1. Patient Data

	Saline (n = 8)	Aminophylline (n = 9)
Age (yr)	27.1 ± 3.4	33.8 ± 4.7
Weight (kg)	61.5 ± 4.5	61.6 ± 2.9
Sex (male/female)	4/4	4/5
Duration of operation (min)	33.3 ± 5.9	28.1 ± 4.2
Duration of anesthesia (min)	114.2 ± 8.7	127.3 ± 9.1

Data are expressed as mean ± SEM.

Monitoring and Measurements

Blood pressure and heart rate measurements were made before and after the injection of flunitrazepam, at 5-min intervals during the operation, and before and after the injection of placebo or aminophylline. The degree of sedation was assessed on a scale from 0–3: 0 indicated no sedation; 1, calm and sedated; 2, asleep but easily arousable; and 3, asleep and unresponsive. Observations were made by an anesthetist unaware of the patient's randomized group after the patients were given flunitrazepam, before they were given saline or aminophylline, and 15, 45, and 75 min after injection of saline or aminophylline.

Amnesia was assessed by showing the patients five memory cards, each depicting a single object. Patients were then asked to identify each card 30, 60, and 90 min after the injection of saline or aminophylline. On the first postoperative morning patients were also asked to recall the objects on the memory cards that they were shown the day before.

The Trieger test was used to assess psychomotor function. Each patient was given the test three times by the same nurse anesthetist at 30-min intervals after the injection of placebo or aminophylline. Whether the patients received 0.9% saline or aminophylline was unknown to the nurse who administered the tests.

Patients were observed for hypotension and respiratory depression intraoperatively. They were asked about retrograde and anterograde amnesia after the tests were completed. Student's t-test and χ^2 test were used for the statistical analysis of the results. Values are expressed as means ± SEM.

Results

Both groups were comparable with regard to patient age, patient weight, and male to female ratio. The mean duration of operation and anesthesia was similar in both groups (Table 1). In group B aminophylline, 2 mg/kg, did not produce statistically significant ($P > 0.05$) changes in blood pressure and heart rate (Table 2).

Table 2. Mean Arterial Pressure and Heart Rate after Flunitrazepam and Aminophylline

	Mean arterial pressure	Heart rate
Baseline		
Group A	91.8 ± 3.7	91.3 ± 1.1
Group B	91.5 ± 6.5	86.2 ± 1.4
After flunitrazepam		
Group A	88.5 ± 3.4	85.0 ± 2.0
Group B	88.3 ± 7.6	82.3 ± 0.8
After saline		
Group A	85.2 ± 4.0	88.2 ± 2.1
After aminophylline		
Group B	85.4 ± 5.5	85.5 ± 1.4

Values are not significantly different ($P > 0.05$) from each other or from controls. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Values are ±SEM.

Sedation

A mean of 1.38 ± 0.07 and 1.41 ± 0.05 mg flunitrazepam was required in groups A and B, respectively, to produce a sleepy state. Flunitrazepam produced sleep within a mean of 3.3 ± 0.4 min after intravenous injection. With the doses employed in this study no statistically significant changes were recorded in blood pressure and heart rate (Table 2). Patients in group B, who were given aminophylline, were less sedated at 15 ($P < 0.01$) and 45 min ($P < 0.05$) than patients given placebo (group A, Fig. 1). Seventy-five minutes after the injection of placebo and aminophylline, the degree of sedation did not differ significantly ($P > 0.05$) between the two groups.

Amnesia

Flunitrazepam produced anterograde amnesia in six (75%) patients in group A and in eight (89%) patients in group B. Patients in both groups did not differ regarding the recall of operation ($P > 0.05$, Fisher's Exact χ^2 test; Table 3). Three patients (38%) given placebo and six (67%) patients given aminophylline remembered being shown postcards after the operation but this difference was not statistically significant ($P > 0.05$, Fisher's Exact χ^2 test; Table 3). Thus, aminophylline did not significantly affect the amnesic effects of flunitrazepam.

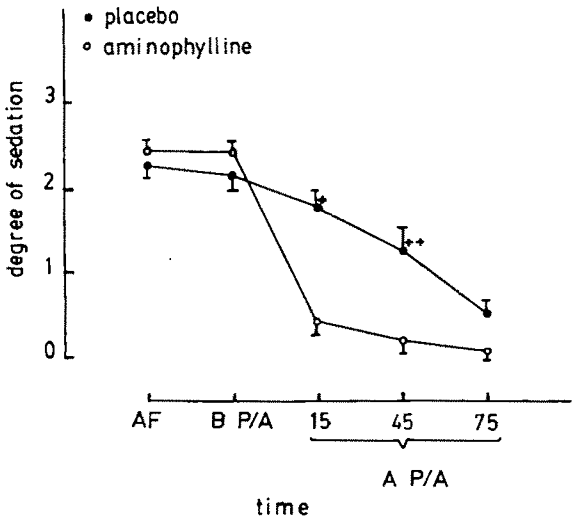

Figure 1. The mean degree of sedation in the aminophylline group was significantly less 15 and 45 min after injection. AF, after flunitrazepam; B P/A, before placebo or aminophylline; A P/A, after placebo or aminophylline; $^{+}P < 0.01$; $^{++}P < 0.05$.

Psychomotor Function

Mean Trieger scores are shown in Figure 2. The number of dots missed by patients in group B was significantly ($P < 0.05$) less than those missed by group A at each point.

Discussion

This study demonstrates that aminophylline given in low doses intravenously antagonizes the sedative and psychomotor effects of flunitrazepam but appears to be ineffective in reversing the strong anterograde amnesia produced by this potent benzodiazepine derivative. It has been reported that flunitrazepam is associated with a long duration of action and a wide individual variation in response (6). In a pilot study we have undertaken in 28 patients we noted that 0.02 mg/kg flunitrazepam did not produce the same level of sedation in all subjects; 13 patients became lightly sedated, 12 were asleep, one was deeply sedated, and two patients became restless and required thiopental for sedation. Therefore, in the present study loss of eyelid reflex was chosen as the criterion of uniform sedation in all cases. The doses that produced sleep in all patients ranged from 0.8 to 3.2 mg.

In group B, 15 and 45 min after the injection of aminophylline the patients were significantly less sedated than those patients in the control group (Fig. 1). About 100 min after the injection of flunitrazepam the level of sedation did not differ significantly between the two groups. During the last assessment of sedation most patients were still free of postoperative pain because the spinal anesthesia was still effective (Table 1). Thus, the steady level of sedation was not affected by postoperative pain after anorectal surgery.

Table 3. Evaluation of Amnesia Produced by Flunitrazepam

Recall	Saline ($n = 8$)	Aminophylline ($n = 9$)
Operation	2*	1
Memory cards	3*	6

*$P > 0.05$ compared with data for aminophylline (χ^2 test).

Flunitrazepam has been reported to be associated with marked anterograde amnesia in adults (7). In the present study most patients in both groups failed to remember the operation. No statistically significant difference was found between the two groups regarding the recall of visual memory cards (Table 3). Thus, aminophylline does not reverse the amnesic effects of flunitrazepam.

The Trieger scores reflecting the psychomotor function were significantly higher at each time of measurement in patients given aminophylline. It is noteworthy that patients in both groups were equally sedated 100 min after the injection of flunitrazepam (Fig. 1). However, the Trieger scores revealed that the psychomotor function was still significantly impaired in the group that was given saline, not aminophylline (Fig. 2).

The sedative properties of benzodiazepines have been said to represent facilitation of GABA-ergic transmission in the cortex (8). Mechanisms other than GABA potentiation have also been proposed to explain the sedative effects of these agents; benzodiazepines, for example, also increase the activity of adenosine, which depresses neuronal activity by reducing the release of neurotransmitters (9). Naturally occurring methylxanthines behave as competitive antagonists of adenosine (10). The results obtained in this study suggest that this may be the underlying mechanism of inhibition of flunitrazepam sedation by aminophylline.

Methylxanthines stimulate the medullary respiratory centers. This action is observed in Cheyne–Stokes respiration (11) and in apneic attacks in the newborn (12). In this study five patients regained consciousness after a deep breath as aminophylline was being injected.

Flunitrazepam is a hypnotic compound (13) that reportedly has cardiovascular effects comparable to those of diazepam (14). The doses of flunitrazepam required to produce a sleepy state in our patients did not result in significant cardiorespiratory depression.

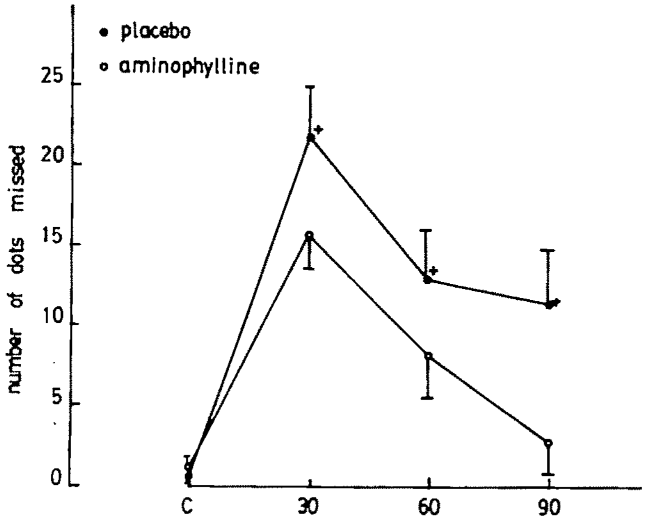

Figure 2. The mean number of dots missed during the Trieger test by the aminophylline group was significantly less than the number missed by the control group at each time of measurement. $^+P < 0.05$.

Aminophylline has been reported to be effective in reversing benzodiazepine sedation in low doses (2–4). Larger doses are known to cause significant alterations in blood pressure and heart rate. In the present study we chose to administer aminophylline in low doses to avoid cardiocirculatory side effects (Table 2).

We conclude that flunitrazepam-induced sedation is of long duration and not appropriate for short surgical procedures. However, it may be reversed by low doses of aminophylline when surgical procedures are completed sooner than expected.

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Blood Levels of Mepivacaine during Continuous Epidural Anesthesia

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Venous blood concentrations of mepivacaine were measured in 30 patients during 5 hr of surgical anesthesia following either multiple epidural injections of mepivacaine with or without epinephrine or continuous epidural infusion of mepivacaine with epinephrine. Patients were divided into three groups: group 1 initially received 10 or 15 ml followed by 10 ml of 2% plain mepivacaine at 1-hr intervals; group 2 received 10 or 15 ml followed by 10 ml of epinephrine-containing 2% mepivacaine at 1-hr intervals; group 3 received 10 or 15 ml followed by a constant infusion of 10 ml/hr of epinephrine-containing 2% mepivacaine. There were no significant differences between groups 1 and 2, but the mean blood concentration was slightly lower for the first 3 hr in group 2 than group 1. The mean blood concentration of mepivacaine in group 3 remained significantly lower than the concentrations in groups 1 and 2 from 3.5 to 5 hr. These results demonstrate that the blood concentrations of mepivacaine are not reduced by the addition of epinephrine to mepivacaine solutions when intermittent epidural injections are repeated more than four times at 1-hr intervals, but that blood mepivacaine levels are reduced below levels seen with intermittent injections by the continuous epidural infusion of epinephrine-containing mepivacaine.

Key Words: ANESTHETICS, LOCAL—mepivacaine. ANESTHETIC TECHNIQUES—epidural.

Epidural anesthesia can inhibit or prevent most of the endocrine-metabolic responses associated with lower abdominal surgery and can suppress to some degree stress responses associated with upper abdominal surgery (1,2); therefore, epidural anesthesia alone or in combination with light general anesthesia has been employed not only for lower abdominal or lower extremity surgery but also for upper abdominal surgery. However, multiple epidural injections of local anesthetics at short intervals result in rapid increases in blood levels of local anesthetics. Following seven repeated injections of mepivacaine at 1-hr intervals, for example, a steady-state level of 7–8 μg/ml mepivacaine in whole blood is achieved (3). Epinephrine is added to local anesthetic solution to decrease the rate of vascular absorption and prolong the duration of anesthesia. The peak blood level of local anesthetic agent is reduced by the addition of epinephrine. However, the effect on systemic blood levels of local anesthetics achieved by adding epinephrine to local anesthetics has not been studied when repeated injections are made, as in prolonged epidural anesthesia. Similarly, although the continuous epidural infusion of local anesthetic agent has been employed for postoperative pain relief (4), but rarely for surgical anesthesia, comparison of the blood concentrations following multiple intermittent injections and continuous infusion of local anesthetics into the epidural space has not been made.

The purpose of the present study is to compare the blood concentrations of mepivacaine following multiple epidural injections of mepivacaine solution with or without epinephrine, and to compare mepivacaine blood levels following multiple intermittent injections and the continuous epidural infusion of mepivacaine solutions with epinephrine.

Methods

Subjects

Thirty adult patients scheduled for epidural anesthesia or epidural plus general anesthesia that would last more than 5 hr were selected for this study. The study was approved by our institution's human research review committee and oral consent was obtained from each patient. The operations performed are presented in Table 1. Patients were randomly divided into three groups of ten each: patients in group

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Table 1. Details of Operative Procedures Performed with Epidural Alone or Epidural Plus General Anesthesia

Procedure	Number
Gastrectomy	8
Proctectomy	5
Pancreato-duodenectomy	2
Pancreatectomy	1
Nephrectomy	3
Nephrolithotomy	1
Cystectomy and ileal conduit	5
Hysterectomy	3
Plastic operation on leg	2

1 received intermittent injections of plain mepivacaine solution into the epidural space; patients in group 2 received intermittent injections of epinephrine-containing mepivacaine solution; and patients in group 3 received a continuous infusion of epinephrine-containing mepivacaine solution.

Epidural Block

All patients were premedicated with 50–100 mg of hydroxyzine and 0.4–0.5 mg of atropine intramuscularly, 1 hr before induction of anesthesia. Further sedation, with 15–30 mg of pentazocine intramuscularly, was given to 14 patients. An intravenous cannula was placed for fluid administration and a central venous catheter was inserted via the antecubital or internal jugular vein for measurement of the central venous pressure and for collection of blood samples.

With the patient in the lateral decubitus position and with 2–3 ml of 1% mepivacaine solution for local anesthesia, the epidural space was entered using a 17-gauge Tuohy needle at the T9-10–L2-3 interspace. According to age, height, and scheduled operation, initial volumes of 10 or 15 ml of 2% mepivacaine without epinephrine in group 1 and with epinephrine in groups 2 and 3 were injected at a rate of 0.5 ml/sec into the epidural space in all patients. A test dose was not used. In groups 1 and 2, supplementary volumes of 10 ml of 2% mepivacaine with or without epinephrine were injected through the epidural catheter at 1-hr intervals for a total of six injections. In group 3, 2% mepivacaine with epinephrine was continuously infused at a rate of 10 ml/hr for 5 hr immediately following the initial injection. Epinephrine 1:200,000 was freshly added to the mepivacaine solution. Ten to 15 spinal segments of analgesia were produced 20 min after the initial injections, as assessed by pinprick.

Intraoperatively, patients were given intermittent intravenous injections of 5–10 mg of diazepam and/or 15 mg of pentazocine, and received oxygen via a face mask. Five patients in group 1, four in group 2, and six in group 3 had inhalation anesthesia consisting of nitrous oxide, oxygen (4:2 L/min) and 0.2–0.5% halothane after induction with 4 mg/kg of thiamylal and tracheal intubation following 1 mg pancuronium and then 1 mg/kg succinylcholine. In 13 patients with arterial cannulae and general anesthesia, ventilation was adjusted to control Pa_{CO_2} between 35 and 45 mm Hg and arterial pH between 7.35 and 7.45. Electrocardiogram, rectal or esophageal temperature, and urinary volume were monitored, and arterial and central venous pressures were measured throughout the operation. Blood loss was replaced as necessary.

Blood Sampling and Analysis

Venous blood samples of 1.5 ml were taken through the central venous catheter with a heparinized syringe before and at 30-min intervals after the initial injection of mepivacaine for 6 hr in groups 1 and 2 and for 5 hr in group 3. The samples were stored at −20°C until measurement of mepivacaine levels by gas chromatography (5). The internal standard used was bupivacaine. The whole blood concentrations of mepivacaine are expressed as μg mepivacaine/ml whole blood.

The data were expressed as mean ± SEM. The results of repeated measurements and multiple groups were analyzed by analysis of variance (ANOVA) and repeated measures ANOVA. Multiple pairwise comparisons between groups were assessed by a Tuckey's or Newman-Keuls' test. $P < 0.05$ was considered statistically significant.

Results

Patient data are summarized in Table 2. During the 5-hr period of this study, blood loss was 784 ± 157 ml, 836 ± 80 ml, and 944 ± 211 ml in groups 1, 2, and 3, respectively, these losses not being significantly different in the three groups. Six patients in group 1 and five each in groups 2 and 3 received initial volumes of 15 ml of 2% mepivacaine solution. Other patients received initial injections of 10 ml. No patients had signs of local anesthetic toxicity during or after surgery.

The mean venous blood concentrations of mepivacaine in each group are shown in Figure 1. Blood mepivacaine concentrations were not significantly different in groups 1 and 2. However, the mean blood concentration in group 2 was slightly lower than that in group 1 for the first 3 hr. Following the fifth dose, blood mepivacaine concentrations approached 7 μg/ml in both groups. The mean maximum concentration in

Table 2. Details of Patients Studied

Group	Sex M/F	Age (yr)	Weight (kg)	Height (cm)
1: Intermittent injection without epinephrine	7/3	55.5 ± 4.0	48.1 ± 2.2	154.3 ± 2.9
2: Intermittent injection with epinephrine	4/6	56.8 ± 4.7	51.7 ± 2.4	153.7 ± 2.6
3: Continuous infusion with epinephrine	5/5	49.6 ± 3.8	55.6 ± 2.9	159.0 ± 3.0

Values are mean ±SEM. No significant differences between groups by analysis of variance.

group 1 was 7.67 ± 0.85 μg/ml at 5.5 hr and in group 2 7.74 ± 0.61 μg/ml at 4.5 hr.

The mean blood concentration of mepivacaine in group 3 increased significantly slowly after the initial rise. It was significantly lower than the mepivacaine level in group 1 at 1.5 and 2.5 hr and from 3.5 to 5 hr, and significantly lower than the level in group 2 from 3.5 to 5 hr. The mean maximum concentration in group 3 was 4.65 ± 0.55 μg/ml at 5 hr.

Discussion

A potential problem associated with continuous epidural anesthesia provided by an intermittent administration of local anesthetic agent is excessive blood level of the agent. The addition of epinephrine to local anesthetic solution decreases the peak blood level of the local anesthetic. In this study, mean blood concentrations following the first to third doses of epinephrine-containing mepivacaine were slightly lower than those obtained with plain mepivacaine, although we compared the mean venous blood concentrations 30 and 60 min after the injections. However, the mean blood concentrations following the fourth to sixth doses of epinephrine-containing mepivacaine were not lower than those obtained with plain mepivacaine. When intermittent epidural injections are repeated at 1-hr intervals more than four times, the effect of epinephrine on the blood mepivacaine concentration disappears. The addition of epinephrine to mepivacaine solution is not necessary in order to decrease the blood level of mepivacaine in patients undergoing operations lasting more than 3 hr.

The mean blood concentration following continuous epidural infusion of epinephrine-containing mepivacaine was very low as compared with intermittent injections. We recommend the use of this technique for long operations to decrease the mean blood level of local anesthetics such as lidocaine or mepivacaine, if longer-acting agents are not used. The continuous epidural infusion of mepivacaine after the initial injection can produce the same range of analgesia that intermittent injections produce (unpublished observations).

The blood concentrations of local anesthetics during continuous epidural anesthesia were predicted by Tucker and Mather (6). They indicated that blood levels increase more rapidly with short-acting agents than with long-acting agents during multiple epidural injections. Tucker et al. (7) subsequently reported close agreement between the predicted and observed plasma concentrations of lidocaine during five epidural injections. In their study, the initial 20 ml of 2% plain lidocaine solution was followed by 10 ml at 1-hr intervals for 4 hr in six patients. The mean maximum plasma concentration of lidocaine was 3.80 ± 0.39 μg/ml, which occurred at 10–30 min after the fifth dose. Bonica et al. (8) also reported the blood concentrations of lidocaine after several epidural injections. With subsequent injections, the maximum blood concentrations increased above those of preceding injections, the final values ranging from 4.0 to 6.65 μg/ml. With regard to mepivacaine, in addition to our previous report (3), there is a study of blood concentrations after three or four caudal epidural injections of 20–30 ml of 1.5% mepivacaine for vaginal delivery (9). The blood mepivacaine concentrations in that study increased above the previous level with each subsequent injection, the final values ranging from about 5 to 11 μg/ml. These blood concentrations are higher than those found in the present study. Although plasma levels after caudal block are higher than after thoracic or lumbar epidural injection (10,11), we cannot compare our data with those reported by Moore et al. (9) because of differences in the site of injection, dose, dosing interval, and other conditions.

The present study was carried out during elective surgery. We excluded patients with hepatic or cardiac disease. Also, although the blood mepivacaine concentrations are influenced by many factors, such as blood volume, cardiac output, hepatic blood flow, local perfusion pressure, arterial pH, and serum protein (10), in our patients there were no differences in body build or blood loss in the three groups.

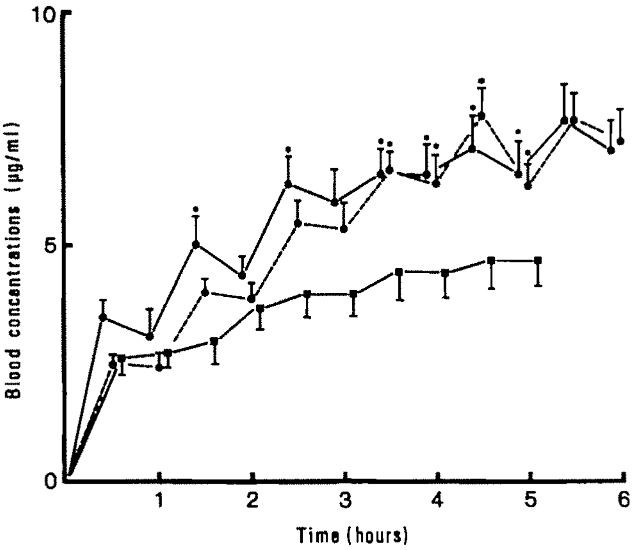

Figure 1. Mean blood concentrations (±SEM) of mepivacaine during epidural anesthesia induced by intermittent injections of 2% plain mepivacaine solution (●—●, group 1), intermittent injections of epinephrine-containing 2% mepivacaine solution (●—●, group 2), or continuous infusion of epinephrine-containing 2% mepivacaine solution (■—■, group 3).
*Statistical significance compared with group 3 ($P < 0.05$).

The toxic threshold for blood mepivacaine is about 6.27 μg/ml (12). Concentrations above this level are often associated with mild cerebral symptoms, including apprehension, confusion, shivering, muscular twitching, nausea, and vomiting. Under light general anesthesia with thiopental and nitrous oxide, the threshold increases to approximately 10 μg/ml for lidocaine (13). We assume a similar increase in toxic threshold for blood mepivacaine concentration during general anesthesia. In our study, none of the patients, all either heavily sedated or under light general anesthesia, had signs of local anesthetic toxicity even though the cumulative dose used amounted to 1200–1300 mg and the blood mepivacaine concentrations exceeded 10 μg/ml in four patients of groups 1 and 2. Moore et al. (9) have suggested that 1000 mg is a maximum safe cumulative dose of mepivacaine for continuous caudal block and that a total dosage of more than 1500 mg should not be used. However, following repeated epidural injections of mepivacaine at 1-hr intervals, a steady-state blood level of 7–8 μg/ml is achieved (3). Using plain mepivacaine solution, a steady-state blood level is achieved more rapidly, as shown in the present study.

When a continuous epidural block is maintained with a constant infusion of mepivacaine, the blood levels increase very slowly. In this study, cumulative doses administered epidurally were equal in the three groups, but the mean blood concentrations of mepivacaine with continuous epidural infusion of mepivacaine with epinephrine were significantly lower than those associated with intermittent epidural injections of mepivacaine with or without epinephrine. Absorption of local anesthetics from the epidural space is related to the vascularity at the site of injection (10). The wide spread of local anesthetics in the epidural space induced by an intermittent injection of a large volume increases the surface area available for absorption. Constant epidural infusion, on the other hand, would not increase the surface area for vascular absorption. Therefore, local accumulation within the epidural space should be greater with a constant epidural infusion of mepivacaine.

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Clinical Reports

Epidermolysis Bullosa:

Anesthetic Management for Cesarean Section

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In a period of 1 month two patients with epidermolysis bullosa (EB) presented for elective cesarean section at our hospital. This unusual condition is associated with problems and potential complications in anesthetic management. Because of the pecularities of EB and the paucity of literature on regional anesthesia with this condition, we report these cases.

Case Reports

Case 1

A 30-yr-old, primagravida white woman, 38 weeks pregnant, presented for elective cesarean section. She had a history of simple generalized EB proven by skin biopsy and evidence of dominant inheritance of EB.

The patient's history was significant for a previous cervical dilatation and curettage and bifid uterus repair under general anesthesia at an outside hospital. She reported a sore throat for 48 hr after her bifid uterus repair as her only complication from general anesthesia. Her only medication was vitamins. Physical examination was unremarkable except for a hypertrophic scar at the site of her skin biopsy 8 months previously. The hematocrit was 39%. We chose a spinal anesthetic to avoid the potential complications of oral instrumentation and tracheal intubation. An 18-gauge IV was started by the obstetric service and wrapped with gauze bandage (Webrol) rather than adhesive tape to hold it in place. The patient was taken to the operating room where she received 1.5 L lactated Ringer's solution intravenously. A blood pressure cuff was applied to the right arm after being padded with Webrol. The patient was placed in the left lateral decubitus position and 7 mg tetracaine in 5% dextrose was injected intrathecally at the L4-5 interspace with a 25-gauge spinal needle. The patient was turned supine and a roll was placed under the right hip. A precordial stethoscope was placed with no adhesive. Electrocardiogram electrodes with no adhesive were placed over the upper scapulae on the patient's back and padded to hold them in place. A third ECG electrode was placed on the patient's right arm and wrapped in place. The patient developed a T-6 sensory level and surgery proceeded without incident.

Vital signs remained stable throughout the procedure. The infant had Apgar scores of 8 (1 min) and 9 (5 min). No bullae were formed as a result of the spinal, the IV, the ECG electrodes, or the blood pressure cuff. The patient had an uneventful postoperative course and was discharged on the ninth postoperative day with small bullae around the nipples due to breast feeding. The infant had no bullae at birth and had not developed any at the time of the 5-month checkup.

Case 2

A 17-yr-old term primagravida woman was admitted to the obstetric service in labor. As a child she had been diagnosed as having dominant dystrophic EB. On physical examination her skin was noted to be moderately scarred and she had alopecia. She did not have nail dystrophy, milia formation, pseudosyndactyly, or gross bullae at initial presentation. The remainder of her physical examination was within normal limits. Prenatal vitamins were her only medication, and she was not aware of allergies to any medication. Her anesthetic history was significant only for an appendectomy as a child under general anesthesia without sequelae.

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The patient was first seen by us when she had 2-cm cervical dilatation and after she expressed a desire for a continuous epidural block for labor pains. After obtaining informed consent, we elected to insert an epidural catheter when the cervix became 4 cm dilated. At that time an 18-gauge intravenous catheter was inserted and secured with Webrol, and a blood pressure cuff applied after the arm was wrapped with soft cotton padding. The patient was placed in left lateral decubitus and the lumbosacral spine was cleaned with an antiseptic (Betadine) spray. The back was draped and the L4-5 interspace and skin were injected with 1% lidocaine. An 18-gauge Hustead needle was inserted, and, using the loss of resistance technique, the epidural space identified. A 20-gauge epidural catheter was inserted 12 cm without difficulty. Collodion was applied to the insertion site, and the catheter was triple looped and fastened to the skin with two 4-0 silk stitches. The catheter was further secured by wrapping the site (around the abdomen) with 10-cm Webrol.

After a negative aspiration and appropriate test doses, 5 ml of 0.375% bupivacaine was injected via the catheter, which was then attached to a 0.1% bupivacaine infusion at 10 ml/hr.

The patient was comfortable throughout labor until her cervix dilated to 10 cm and the fetus was at zero station. She remained in this state and a diagnosis of primary cephalopelvic disproportion, secondary to midpelvic contraction, was made. The patient was then scheduled for a Kerr cesarean section (transverse lower uterine segment). She was positioned on the surgical table, which was then tilted to the left. The epidural catheter was again aspirated prior to a test dose of 3 ml of 1.5% lidocaine with 1:200,000 epinephrine. A T-6 sensory block was established with 20 ml of 2% lidocaine. Electrocardiogram electrodes were modified by cutting off all but 0.5 cm^2 adhesive on opposite sides of the circular patch. Blood pressure was monitored as described above, and a pediatric precordial stethoscope was placed over the precordium without tape. Surgery proceeded uneventfully and the postoperative period was uncomplicated. This infant had the same Apgar scores of 8 (1 min) and 9 (5 min) as in case 1. The infant had no bullae at birth and no evidence of congenital problems.

Discussion

Epidermolysis bullosa (EB) is a group of genetically determined disorders characterized by blistering of the skin and certain mucosal membranes. The blisters arise spontaneously or as the result of minor trauma. Trauma to the skin in a parallel direction (as in rubbing) is more damaging than trauma in a perpendicular direction.

Several syndromes plus several variants are described. Recently electron microscopy has aided differentiation of the syndromes, but classification is primarily clinical. The syndromes are classified as scarring and nonscarring (1).

Dominant simple generalized EB, a nonscarring form, has automosal dominant inheritance, with an incidence of 1/50,000 live births. Bullae are formed by the disintegration of basal and suprabasal cells. General physical development, as well as the hair, nails and teeth, are normal. Bullae usually develop in the first year of life and are most noticeable in areas of trauma such as the hands and feet. The condition persists throughout life but some cases have improved after puberty. The oral mucous membranes may be involved.

Epidermolysis bullosa lethalis and simple localized EB are other examples of nonscarring EB. Epidermolysis bullosa lethalis is a more serious disease and is recessively inherited. This disease is evident at birth and most individuals die by the age of 3 months from fluid loss and infection. Localized EB involves primarily the hands and feet but is otherwise similar to generalized EB.

Dominant dystrophic EB and recessive dystrophic EB are examples of scarring EB. Recessive dystrophic EB is the more severe form with most affected individuals dying by their second decade. This disease leads to clublike, or loss of, limbs. Recurrent bullae of the esophagus are frequent and may lead to esophageal stricture. Anemia and malnutrition are common also. Treatment is primarily symptomatic but steroids and phenytoin have been used to reduce bullae formation.

Anesthetic management of patients with EB is directed toward avoiding trauma to the skin and mucous membranes. Trauma from adhesive tape, blood pressure cuffs, tourniquets, adhesive ECG electrodes or rubbing with alcohol wipes may cause bullae formation. Alcohol sponges may be used without rubbing. If a blood pressure cuff is used, it should be padded. Intraarterial or intravenous catheters should be sutured in place or held in place by a gauze wrap. Oropharyngeal and nasopharyngeal airways as well as esophageal stethoscopes should be avoided if possible, as they may lead to intraoral or intraesophageal bullae and bleeding (1). Bleeding from ruptured oral bullae has been treated successfully by epinephrine-soaked gauze applied to the bullae (2). Trauma from face masks is also a potential problem. Masks should have a soft air cushion and be coated with lubricant-soaked gauze. In addition, the jaw should be covered with lubricant-soaked gauze where the fingers rest (1,3). Ketamine–diazepam anesthesia has been reported to be advantageous in patients with EB. Respiration can be spontaneous and thus manipulation of the patient's airway is minimal (4).

A large series of EB patients who had general anesthesia with endotracheal intubation has been reported, oral intubation being found to be relatively safe with only occasional intraoral bullae formation (5). Some patients with scarring EB may have a small scarred mouth and prove to be difficult to intubate. When intubation is necessary, generous lubrication of the laryngoscope and endotracheal tube is needed, and a smaller size tube than predicted should be used (1,3,5). Laryngeal involvement with recurrent airway obstruction has been reported in a patient with recessive dystrophic EB (6). This complication is apparently rare and there are no reports of tracheal involvement.

Although avoidance of local anesthetic infiltration in EB patients has been recommended (7), we successfully used local skin infiltration in case 2 without bullae formation. If bullae do develop, they often become infected, usually by *Staphylococcus aureus* or B-hemolytic Streptococci.

Several diseases have an increased incidence in patients with EB. Among these are porphyria, congenital pyloric atresia, amyloidosis, multiple myeloma, diabetes mellitus, and hypercoagulable states. Anemia, electrolyte abnormalities and malnutrition are common coexisting problems. Screening for porphyria is recommended by several authors before a general anesthetic because of the common use of barbiturates for induction. Other suggested preoperative laboratory tests include complete blood count, serum protein levels, urinalysis, electrolytes, and blood urea nitrogen (8).

In summary, we report two patients with EB who underwent cesarean section. They were successfully anesthetized with regional anesthesia, and we give a brief review of suggested anesthetic management for these difficult patients. We believe regional anesthesia should be considered in EB patients to prevent airway manipulation.

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Sudden Intraoperative Hypotension in a Patient with Asymptomatic Urticaria Pigmentosa

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Urticaria pigmentosa is a usually benign and asymptomatic cutaneous variant of mastocytosis, a disorder distinguished by abnormal proliferation of tissue mast cells (1,2). Infrequently, the systemic variant of mastocytosis, characterized by abnormal, secretory mast cell aggregations in visceral organs and bone, may be concomitantly found in patients with urticaria pigmentosa (3). These abnormal aggregations, if present, can abruptly release vasoactive mediators such as histamine and prostaglandin D_2 and produce acute, profound hypotension. Precipitating factors of release are unclear in most instances.

Although cardiovascular instability during the anesthetic management of patients with symptomatic systemic mastocytosis has been documented (4), there have been no reports of hemodynamic instability during the anesthetic management of patients with previously asymptomatic urticaria pigmentosa. We report a case of profound intraoperative hypotension in an adult patient with asymptomatic urticaria pigmentosa to emphasize to anesthesiologists the association of urticaria pigmentosa and systemic mastocytosis.

Report of a Case

A 70-yr-old, 72-kg, white female was scheduled for abdominal resection of a grade 1 adenocarcinoma of the rectum. Her past medical history included 20 yr of osteoporosis with compression fractures of the bodies of T-11, L-2, and L-5. In addition, urticaria pigmentosa had been diagnosed in 1981 by forearm skin biopsy. The small, red-brown maculae characteristic of urticaria pigmentosa first appeared 3 yr prior to the diagnosis and had been asymptomatic. The patient had undergone three colonic polypectomies under intravenous sedation from 1981 to 1985 and a left modified radical mastectomy under general anesthesia in 1984. She had no difficulties with previous anesthetics. Flexible sigmoidoscopy performed under intravenous sedation 1 week prior to her surgery revealed a 1-cm sessile polyp at 22 cm containing an adenocarcinoma.

Preanesthetic examination revealed multiple pigmented maculae on her trunk and upper extremities and a grade 2/6 murmur at the cardiac apex. The remainder of her physical examination was normal. Preoperative laboratory results, including a white blood cell differential count, were within normal limits. An ECG and chest roentgenogram were unremarkable.

With the usual monitoring, including mass spectrometry, pulse oximetry, and indirect measurement of blood pressure by sphygmomanometer and cuff, anesthesia was induced with thiopental 4 mg/kg intravenously. Tracheal intubation was facilitated with succinylcholine, 1.5 mg/kg, intravenously. Anesthesia was maintained with enflurane and nitrous oxide at an F_{IO_2} of 0.5 and supplemented with oxymorphone, 1 mg, intravenously. Further muscle relaxation was achieved with metocurine, 8 mg, intravenously after spontaneous return of neuromuscular activity from the succinylcholine-induced blockade. Approximately 90 min after anesthesia was induced and the last intravenous drugs were given, the patient became acutely hypotensive with a systolic blood pressure of 50 mm Hg and had generalized flushing. Prior to this episode, she had received no blood products and the tumor had been excised. The etiology of the hypotensive episode was uncertain; however, the patient was treated as if an anaphylactoid reaction had occurred. The initial treatment consisted of an infusion of 2 L of lactated Ringer's solution, a bolus injection and subsequent intravenous infusion of epinephrine to a total dose of 1.5 mg, dexamethasone, 4 mg intravenously, and diphenhydramine, 50 mg intravenously. A pulmonary artery catheter was placed via the right internal jugular vein; the initial pulmonary capillary wedge pressure was 1 mm Hg. A radial artery catheter was placed and an arterial blood analysis at an F_{IO_2} of 1.0 revealed the Pa_{O_2} to be 407 mm Hg, Pa_{CO_2} 44 mm Hg, pH 7.30,

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and base excess −6 mEq/L. For the first 15 min after the onset of flushing and hypotension, manual occlusion of the infrarenal aorta was required to maintain a systolic blood pressure of greater than 50 mm Hg. Twenty-five minutes after the onset of hypotension and flushing, the blood pressure returned to normal and the pulmonary capillary wedge pressure increased to 11 mm Hg. She remained hemodynamically stable and the flushing faded. Surgery was completed and the patient was transferred to the intensive care unit. During the following 36 hr, she remained hemodynamically stable with the support of inotropic agents and the infusion of 7 L of fluid. She was extubated on the second postoperative day and recovered uneventfully.

Discussion

Sudden profound intraoperative hypotension requires an immediate response to the underlying cause. Because the generalized erythema that occurred simultaneously with the onset of acute hypotension in our patient was felt to represent anaphylactoid shock, resuscitative efforts were instituted based on that clinical impression. The underlying etiology was unclear; however, the preoperative presence of urticaria pigmentosa suggested the acute release of vasoactive mediators as a possible etiology.

There are five variants of mastocytosis: urticaria pigmentosa, systemic mastocytosis, solitary mastocytoma, telangiectasia macularis eruptiva perstans, and diffuse cutaneous mastocytosis (1,2). Ninety percent of patients with mastocytosis present with asymptomatic urticaria pigmentosa. The majority of other patients with mastocytosis have systemic mastocytosis. Urticaria pigmentosa, a disease primarily of children, is characterized by multiple, small, red-brown maculae distributed most commonly on the trunk and upper extremities. In most patients, lesions are present within the first year of life. Adults who develop lesions usually do so prior to the age of 20 yr (3). The prognosis generally is quite good, with approximately half of the patients who have urticaria pigmentosa in childhood free of the skin lesions by adulthood. Systemic mastocytosis occurs more frequently in adults and involves visceral organs and, with rare exceptions, the skin. As illustrated by our patient, there is some confluence of the variants of mastocytosis; for example, systemic mastocytosis develops in approximately 15% of patients in whom the skin lesions of urticaria pigmentosa initially appear after childhood (3).

Many of the symptoms of mast cell disease, including pruritis, urticaria, flushing, hypotension, and syncope, have been attributed to histamine released from mast cells (5). However, mast cells are capable of releasing many other clinically significant mediator substances (2). Therefore, controversy exists over the efficacy of histamine$_1$ (H$_1$) and histamine$_2$ (H$_2$) receptor blockade in attenuating the symptoms of mast cell release. In a recent double-blind clinical trial to evaluate the relief of symptoms of mast cell release by treatment with H$_1$ and H$_2$ blocking agents, Frieri et al. (6) were unable to demonstrate any improvement with either H$_1$ or H$_2$ blockade. Prostaglandin D$_2$ may contribute to the hypotension frequently observed in mastocytosis and may account, in part, for the inability of histamine receptor blockade to attenuate this symptom (7). Heparin is another mediator substance released by mast cells. However, hemorrhagic complications are rare (8).

Mediator release can occur via the classic anaphylactic mechanism involving the cross-linking of surface bound IgE or by non-IgE mechanisms. The latter type of response occurs in anaphylactoid reactions. The classic symptoms of mastocytosis are believed to be anaphylactoid in origin. A host of agents have been implicated as stimulators of mediator release and include polymixin, quinine, morphine, codeine, *d*-tubocurarine, gallamine, aspirin, atropine, extremes of temperature, and stress (2).

The major hazard of intraoperative management of patients with mastocytosis or its variants appears to be hemodynamic instability. Parris et al. (9) reported the development of hypotension requiring epinephrine infusions in five of 42 patients with mastocytosis undergoing anesthesia and surgery. However, for the majority of patients with this disease complex, the intraoperative period is benign (9,10). Recommendations for anesthetic management of patients with either urticaria pigmentosa or mastocytosis appear to be empiric based on these reports. The preoperative use of H$_1$ and H$_2$ receptor blocking agents is often recommended (9,10), but their efficacy has not been documented. Similarly, premedication with aspirin has been advocated because of its inhibition of the production of prostaglandin D$_2$ (4), although aspirin has been implicated by some as a triggering agent for mediator release (2). The usefulness of aspirin for this purpose has not been proved. Potent inhalation agents tend to inhibit mast cell degranulation and theoretically may be of benefit (11). Essential to the anesthetic management of a patient with mast cell disease is the ready availability of agents that may be used to treat anaphylactoid shock. In particular, intravenous epinephrine has been demonstrated to be the primary drug effective in reversing the hypotension associated with patients with mastocytosis (12).

In summary, the association of systemic mastocytosis with asymptomatic urticaria pigmentosa in our patient, who was in the seventh decade of life, is unusual. Since her urticaria pigmentosa had been totally asymptomatic prior to surgery, we did not choose to premedicate our patient with histamine receptor blocking agents or aspirin. It is unknown whether such premedication would have avoided the abrupt anaphylactoid reaction seen in our patient. The use of epinephrine in this case was lifesaving. We report this case to alert anesthesiologists to the clinical implications of urticaria pigmentosa and its association with mast cell diseases.

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Dependent PEEP during Two-Lung Ventilation in the Lateral Decubitus Position

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In anesthetized patients in the lateral decubitus position, the dependent lung is less ventilated and more perfused than the nondependent lung, resulting in ventilation–perfusion mismatching (1–3). A physiologic solution to the adverse effects of anesthesia and surgery in the lateral decubitus position on the distribution of ventilation and perfusion would be the application of selective positive end expiratory pressure (PEEP) to the dependent lung (2,3). Selective PEEP to the lower lung may increase ventilation of this lung by moving it up to a steeper, more favorable portion of the lung pressure–volume curve; it may also increase vascular resistance in the lower lung and shift more blood flow to the upper lung.

The present report investigates the effect of selective application of dependent PEEP in patients undergoing radical nephrectomy in the lateral decubitus position. The investigation compares the differential distribution of ventilation between the dependent and the nondependent lungs, as well as the arterial P_{O_2} and P_{CO_2} levels before and after application of the dependent PEEP.

Methods

Selective PEEP was achieved using a single anesthetic machine by dividing the inspiratory and expiratory limbs of the soda-lime absorber by a wide-bore Y piece into two inspiratory and two expiratory limbs. The two circuits were isolated by providing each limb with a unidirectional valve matching the inspiratory and expiratory valves of the machine. Dependent PEEP was selectively achieved by including an Emerson PEEP valve within the expiratory limb of the dependent lung. The tidal volumes exhaled from the dependent lung and the nondependent lung were measured by two Wright spirometers (Fig. 1).

The technique of dependent PEEP during two-lung ventilation was investigated in three patients scheduled for right radical nephrectomy in the lateral decubitus position. Preoperatively, the chest and heart were clinically normal in all three patients. The procedure lasted 3–5 hr, which permitted time for the establishment of a steady state and to use the patients as their own controls.

Patients were premedicated with intramuscular meperidine 100 mg, promethazine 25 mg, and atropine 0.6 mg. Following preoxygenation, anesthesia was induced by thiopental 7 mg/kg, followed by succinylcholine 1.5 mg to facilitate tracheal intubation with a double-lumen bronchial tube (Bronchocath). Each limb of the double-lumen tube was attached to one anesthesia circuit. After the appropriate position of the tube was determined by chest auscultation, it was firmly fixed and the patient turned to the lateral decubitus position with the right side up. Anesthesia was maintained with 50% nitrous oxide: oxygen supplemented by fentanyl 5 μg/kg, with neuromuscular blockade continued by the nondepolarizing muscle relaxant alcuronium.

Ventilation of the two lungs was controlled throughout the procedure by one ventilator using a total exhaled tidal volume of about 15 ml/kg at a rate of 15/min. The driving inspiratory pressure varied between 22 and 28 cm H_2O. After 60 min of bilateral zero end expiratory pressure (ZEEP) ventilation, arterial P_{O_2} and P_{CO_2}, as well as the differential distribution of the tidal volume between the two lungs, were measured. Ten centimeters of H_2O PEEP was then added selectively to the dependent lung, and ventilation of the two lungs was continued using the same total tidal volume and respiratory rate. After 60 min of dependent PEEP, the differential distribution of the tidal volume between the two lungs and the arterial blood gas tensions were measured and com-

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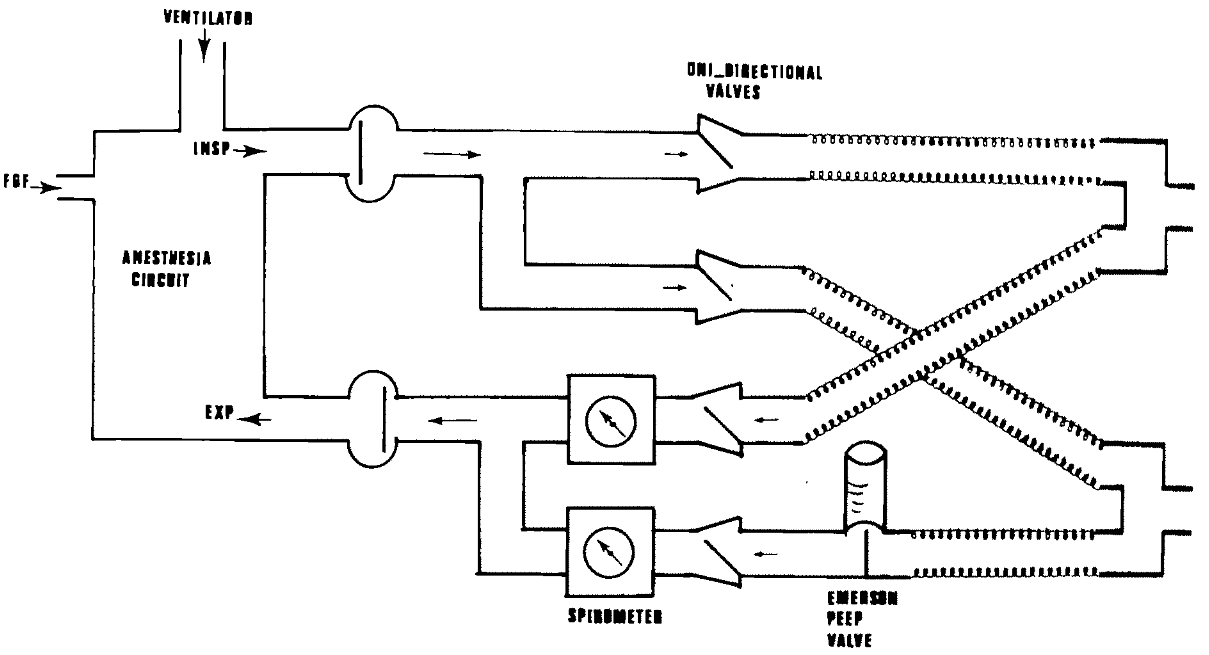

Figure 1. Schematic diagram of the two circuits attached to a single anesthesia machine. An Emerson PEEP valve is installed on the expiratory limb of the dependent lung. Two Wright spirometers are used to measure the exhalation tidal volume of each lung.

pared with values during ZEEP ventilation. The central venous pressure (CVP) was measured in the three patients before and after the application of dependent PEEP. Also, a thermodilution pulmonary artery (Swan-Ganz®) catheter was inserted in one of the patients to compare cardiac output and pulmonary artery pressure before and after application of dependent PEEP.

Results

Distribution of Ventilation

During ZEEP ventilation of the two lungs with a tidal volume of about 15 ml/kg, the peak inspiratory pressure ranged between 22 and 28 cm H_2O. The nondependent lung was preferentially ventilated; about 56% of the tidal volume was delivered to the nondependent lung with only 44% going to the dependent lung. Adding selective PEEP (10 cm H_2O) to the dependent lung while maintaining two-lung ventilation by the same total tidal volume did not change the peak inspiratory pressure. However, dependent PEEP was followed by a further increase in nondependent lung ventilation of up to 63% of the total tidal volume whereas the dependent lung ventilation decreased to 37% of the tidal volume (Table 1).

Arterial Blood Gases

During ZEEP ventilation, the arterial P_{O_2} ranged between 129 and 263 mm Hg, and the arterial P_{CO_2} between 30 and 43 mm Hg. Adding dependent PEEP did not change the P_{CO_2} in the three patients, and was followed by lowering P_{O_2} in one of the patients (Table 1).

Hemodynamic Parameters

Dependent PEEP was followed by an elevation of CVP in the three patients (Table 1). Also, PEEP was followed, in the patient whose hemodynamic parameters were measured, by a decrease of the cardiac output from 6.0 to 5.4 L/min, associated with an increase in the pulmonary artery pressure of from 18/8 to 21/13 mm Hg.

Discussion

In the awake patient in the lateral decubitus position, the dependent lung is better ventilated than the nondependent lung, regardless of the side on which the patient is lying. The preferential ventilation of the dependent lung is matched by its increased perfusion (3).

In anesthetized patients in the lateral position, ventilation is preferentially switched from the dependent to the nondependent lung. This may be related to an anesthesia-induced decrease in functional residual ca-

Table 1. Distribution of Tidal Volume Between Dependent (D) and Nondependent (ND) lungs, Arterial Po_2 and Pco_2, and Central Venous Pressure (CVP) Before and After the Application of Dependent PEEP[a]

Patient				ZEEP ventilation					Dependent PEEP ventilation				
				Tidal volume					Tidal volume				
Sex	Age (yr)	Weight (kg)		ND (ml)	D (ml)	Po_2 (mm Hg)	Pco_2 (mm Hg)	CVP (cm H_2O)	ND (ml)	D (ml)	Po_2 (mm Hg)	Pco_2 (mm Hg)	CVP (cm H_2O)
F	46	104		800	600	263	43	14	900	500	181	40	18
F	56	70		600	500	230	30	8	700	400	228	29	14
M	26	75		625	475	129	35	6	650	450	130	34	11
			Mean	675	525	207.3	36	9.3	750	450	180	43.0	14.3
			SD	109	66.0	69.8	6.6	4.2	132	50	49	5.5	3.5

[a] During ZEEP ventilation, the ND lung received 56% of the tidal volume and the D lung received 44% ($P < 0.05$). After dependent PEEP, the ND lung received 63% of the total tidal volume and the D lung received 37% ($P < 0.05$). The application of PEEP also increased the CVP significantly ($P < 0.02$), but did not produce a significant change of Po_2 and Pco_2 ($P > 0.1$).

pacity (FRC) that moves each lung to a lower but different part of the nonlinear pressure–volume (compliance) curve. The dependent lung moves from an initially steep (compliant) part of the curve to a lower and flat (noncompliant) part, and the nondependent lung moves from an initially flat part of the curve to a lower and steeper part (Figs. 2*A* and 2*B*). Also, the downward pressure of the mediastinum and the weight of the abdominal contents produce further reduction of FRC in the dependent lung and physically impede its expansion (3–5). In contrast to the preferential ventilation of the nondependent lung, the dependent lung is preferentially perfused, resulting in ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatching (2); the nondependent lung is more ventilated than perfused (dead space effect) and the dependent lung is better perfused than ventilated (shuntlike effect). Applying PEEP to the dependent lung can counteract this $\dot{V}/\dot{Q}$ mismatching (2) by increasing the FRC of the dependent lung and moving it up to a steeper and more favorable part of the pressure–volume curve (Fig. 2*C*). It can also counteract the gravitational increased perfusion of the dependent lung and improve perfusion of the nondependent lung (6).

The present report confirms that during the lateral decubitus position in anesthetized patients, the nondependent lung is preferentially ventilated. However, application of selective PEEP to the dependent lung was not associated with an increase in dependent lung ventilation or an improvement of arterial Po_2 and Pco_2. In contrast, there was a further decrease in dependent lung ventilation associated with an increase in nondependent lung ventilation. Although the selective PEEP may increase the compliance of the dependent lung by moving it up to the steep part of the pressure–volume curve, it decreases the pressure difference between the driving inspiratory pressure and the intra-alveolar pressure. This decrease of pressure gradient may offset, or even exceed, the improved compliance of the dependent lung, ventilation thus being switched more preferentially to the nondependent lung ventilated at ZEEP. Also, dependent PEEP increased the CVP in the three patients; it did not improve the arterial Po_2 but was even associated with a marked decrease in Po_2 in one of the patients and by a decrease in cardiac output in a second patient.

Optimal $\dot{V}/\dot{Q}$ matching during two-lung ventilation in the lateral decubitus position by the use of selective dependent PEEP requires differential lung ventilation with even distribution of ventilation between the two lungs (6). Dependent PEEP counteracts the gravitational greater perfusion of the dependent lung, which will be matched by the equal distribution of ventilation between the two lungs. However, dependent PEEP associated with differential ventilation complicates the anesthetic technique by using a double-lumen tube and by the simultaneous use of two anesthesia circuits.

The use of a general (i.e., bilateral) PEEP has been suggested for two-lung ventilation in the lateral decubitus position (7). General PEEP increases FRC in both lungs and hence shifts the nondependent lung to its original position on the flat, noncompliant part of the pressure–volume curve, whereas it improves the compliance of the dependent lung by restoring its position on the steep part of the curve (Fig. 2*D*). However, general PEEP can markedly decrease the cardiac output and exaggerate the gravitational distribution of pulmonary blood flow (6).

As shown by our report, the use of a high F_{IO_2} (0.5) and a large tidal volume (about 15 ml/kg) without PEEP can maintain adequate arterial Po_2 and Pco_2 levels during two-lung ventilation in the lateral decubitus position. The high F_{IO_2} and the large tidal volume may compensate for the $\dot{V}/\dot{Q}$ mismatching

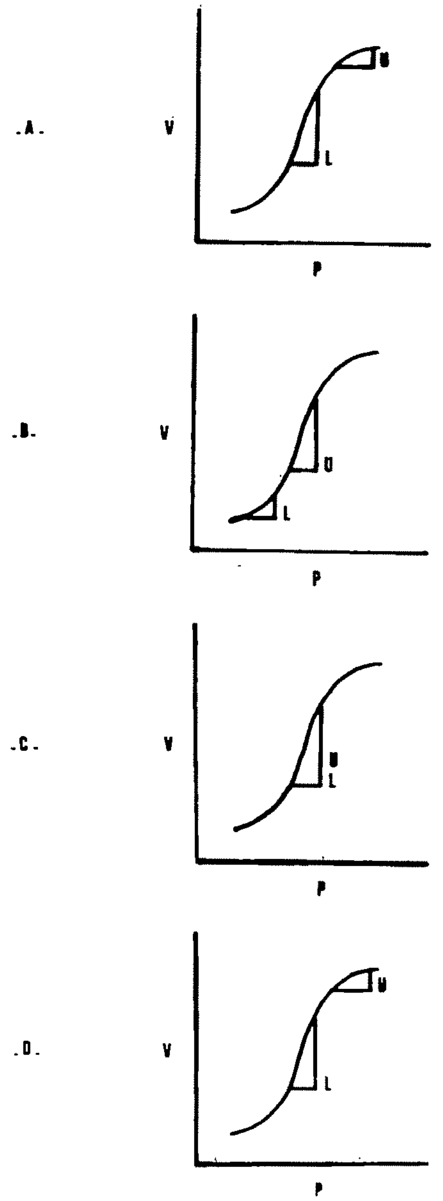

Figure 2. Diagrams showing the pressure (P)–volume (V) curves of the dependent (L) lung and the nondependent (U) lung in the lateral decubitus position. (A) awake patient; (B) anesthetized patient with ZEEP ventilation; (C) anesthetized patient with dependent PEEP ventilation; (D) anesthetized patient with general PEEP ventilation.

secondary to preferential ventilation of the nondependent lung and preferential perfusion of the dependent lung.

In conclusion, during two-lung ventilation of anesthetized patients in the lateral decubitus position, ventilation is preferentially distributed to the nondependent lung. However, the use of a large tidal volume (about 15 ml/kg) and a high $F_{I_{O_2}}$ (0.5) for ventilation can maintain normal arterial P_{O_2} and P_{CO_2} levels. Applying selective dependent PEEP does not increase, and even decreases, dependent lung ventilation, and does not improve oxygenation or carbon dioxide elimination. It is suggested that the use of a high $F_{I_{O_2}}$ and a large tidal volume without PEEP, via an ordinary tracheal tube and a single anesthesia circuit, may compensate for $\dot{V}/\dot{Q}$ mismatch, and hence can be safety used for two-lung ventilation in the lateral decubitus position.

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Safe Use of Succinylcholine during Repeated Anesthetics in a Patient Treated with Cyclophosphamide

Judith B. Dillman, MD

Cyclophosphamide (Cytoxan®), an antineoplastic chemotherapeutic agent related to the nitrogen mustards that have been in use for many years, has recently been employed as a therapeutic agent in an expanding number of diseases. Previously indicated only for the treatment of hematologic and solid tissue cancers, the drug is now being utilized for its potent immunosuppressive properties in nonneoplastic disorders associated with altered immune reactivity, including Wegener's granulomatosis, selected patients with systemic lupus erythematosus and rheumatoid arthritis, and the nephrotic syndrome in children, as well as in patients with autoimmune blood disorders, such as idiopathic thrombocytopenia. It is also being used prophylactically in patients undergoing bone marrow transplantation (1–3).

This increasing use of cyclophosphamide is of potential concern to anesthesiologists because the drug has been reported to inhibit the enzyme plasma(pseudo)cholinesterase (4). In 1967, Mone and Mathie (5) stated that "the chances of patients on cyclophosphamide being exposed to a general anesthetic with suxamethonium may seem remote." If true then, it is less so today, when increasing numbers of patients being treated with cyclophosphamide are presenting for various surgical procedures.

In the early 1960s, meturedepa, known as AB-132, was investigated as a potential antineoplastic agent. After reports of prolonged apnea with succinylcholine administration in patients receiving AB-132 (6), Mone and Mathie (5) tested the pseudocholinesterase levels of eight patients receiving cyclophosphamide 50 mg orally every day and reported a reduction of approximately 50% in pseudocholinesterase activity. Succinylcholine was not administered to any of these patients, and the authors recommended that the drug not be used in patients receiving cyclophosphamide.

In 1972, Zsigmond and Robins (4) reported the in vitro inhibitory effect of cyclophosphamide and three other alkylating antineoplastic agents on plasma cholinesterase. They recommended reduction in the dose of succinylcholine in patients treated with these types of chemotherapeutic agents. In 1972, Walker et al. (7) measured plasma cholinesterase activity in eight patients being treated with cyclophosphamide and found depressed levels in seven of them. Only one patient, however, had surgery. This patient developed apnea attributed to a prolonged effect of succinylcholine, but this was not documented by use of a nerve stimulator.

A search of the literature failed to reveal more recent reports of a potential relationship between cyclophosphamide and pseudocholinesterase activity, and also indicated that the recommendations against usage of succinylcholine were not founded upon actual clinical use with modern neuromuscular monitoring techniques. In this report, we document the successful use of succinylcholine for 16 anesthetics in a patient continuously treated with cyclophosphamide.

Case Report

A 31-yr-old male had been diagnosed as having Wegener's granulomatosis in September 1984. After intravenous therapy with cyclophosphamide for 10 days, the patient was maintained on 125 mg cyclophosphamide orally every day from that time to the date of this report, June 1986. During this 21-month period, the patient had 16 surgical procedures (mostly bronchoscopies and dilations of subglottic stenosis—a sequela of his disease). During each of these surgical procedures, muscle relaxation was maintained with succinylcholine by either intermittent bolus or constant infusion. The extent of neuromuscular blockade was monitored visually by observing movement of the adductor pollicis with supramaximal ulnar nerve stimulation (0.1 Hz). Table 1 lists dosages of succinylcholine used and duration of neuromuscular blockade. Although the patient had a slightly pro-

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Table 1.

Surgical procedure	Total dose of succinylcholine (mg)	Duration of blockade (min)
1	100	30
2	110	50
3	200	26
4	200	30
5	235	43
6	150	20
7	75	20
8	150	15
9	100	22
10	300	30
11	100	25
12	100	55
13	260	45
14	60	25
15	80	15
16	150	15

longed response to succinylcholine, this was never judged to be clinically significant and he was taken to the recovery room after each procedure with good spontaneous respirations.

Cholinesterase activity levels were determined prior to this patient's most recent surgical procedure. The pH Stat method (8) for determination of plasma and red cell cholinesterase activities was utilized. The patient did indeed have a marked reduction in plasma cholinesterase activity with an activity level of 1.23 $\mu mol \cdot min^{-1} \cdot ml^{-1}$, which is about one-third of normal (8). His red cell cholinesterase activity was normal. An atypical form of plasma cholinesterase was excluded by the determination of the dibucaine number (9,10), which was 87%, within normal limits. To exclude more uncommon genetic variants reported by Whittaker (11) and by Lehmann and Liddell (12), which are not detected by dibucaine inhibition, an RO2-0683 inhibition (13) was obtained, which was 73%—again within normal limits. (RO2-0683 is a dimethylcarbamate of (2-hydroxy-5-phenylbenzl)-trimethyl-ammonium bromide, a neostigmine derivative.)

Discussion

This is a clinical report of extended experience with a patient taking cyclophosphamide, yet repeatedly given anesthetics during which muscle relaxation was facilitated with succinylcholine. Despite markedly reduced pseudocholinesterase activity levels, the patient's responses to properly monitored, reduced succinylcholine dosages, although somewhat variable, have not been problematic. The absence of a prolonged response to succinylcholine in this patient is evidence that the genotype, as determined by dibucaine and other inhibitors, is more clinically significant than a quantitative reduction of the typical pseudocholinesterase enzyme.

The variability in this patient's duration of neuromuscular blockade with a given total dose of succinylcholine administered during separate procedures could be attributable to several factors. 1) Without having pseudocholinesterase levels drawn on each occasion, it would be impossible to know the exact enzyme activity present on that day. Maximal plasma concentrations are achieved 1 hr after oral administration of cyclophosphamide, the half-life in plasma of which is about 7 hr (1). Although cyclophosphamide causes irreversible inhibition of the pseudocholinesterase enzyme, the constant synthesis of new enzymes by the liver may result in variations over time in the proportion of pseudocholinesterase that is inhibited. 2) The total dose of succinylcholine necessary for blockade for a given time period would vary according to delivery by constant infusion or intermittent bolus. We were able to avoid prolonged apnea with either method of infusion through the use of a peripheral nerve stimulator.

We conclude that succinylcholine can be administered to patients taking cyclophosphamide, but anesthesiologists should be aware that: 1) there are several new indications for cyclophosphamide that increase the chance that patients presenting for anesthesia may be taking the drug; 2) several of these new indications require short, repeated anesthetics, for which succinylcholine is frequently chosen; and 3) proper neuromuscular monitoring is essential if overdosage and prolonged apnea are to be avoided.

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Hemodynamic Responses Associated with Lithotripsy

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Extracorporeal shock wave lithotripsy (ESWL) for the treatment of kidney and ureteral stones is today a highly popular and widely used alternative to percutaneous nephrolithotomy and surgical removal of urinary stones. Its advantages include a high success rate, low morbidity, shorter hospital stay, and lower cost (1,2).

Because ESWL produces a painful stimulus, general or regional anesthesia is required to prevent not only pain but also movement by the patient that might alter the position of a stone targeted on the image intensifier screen (3). Extracorporeal shock wave lithotripsy requires that the anesthetized patient be immersed in water in a semisitting position while high energy shock waves are delivered to the kidney to crush the stone (4). Anesthesia, immersion in water, and ESWL itself may significantly affect the cardiovascular system and the kidney (3–7), but the cardiovascular responses have not been quantitated in detail. We therefore undertook the present study in 11 patients of hemodynamic changes associated with general anesthesia and ESWL, as measured by a transesophageal Doppler ultrasonic cardiac output monitor, other methods for measuring hemodynamic function being difficult in patients almost totally immersed in water.

Methods and Materials

Hemodynamic responses associated with ESWL were measured in 11 unpremedicated patients, six women and five men, with no known cardiopulmonary disease. The mean age was 53 ± 15 yr (range 31–74), weight 79 ± 21 kg (range 58–119), and height 156 ± 7 cm (range 149–173) (Table 1). A peripheral vein was cannulated and 5% dextrose in lactated Ringer's solution was given at a rate of 6–8 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ to increase urine output and thus wash out pulverized stones from the urinary tract. The electrocardiogram was monitored. Because the ESWL shock wave generator is triggered by the R-wave of the ECG, atropine, 0.3–0.4 mg, was given intravenously to maintain heart rate and shock waves over 80/min.

Eight patients were placed on the lithotripsy chair before the induction of anesthesia. Three patients were anesthetized on a cystoscopy table, their ureteral stones then being pushed into the renal pelvis via a cystoscope before the patients were transferred to the lithotripsy chair for ESWL. Anesthesia was induced in all patients with thiopental, 4–6 mg/kg, followed by intubation with the aid of succinylcholine. After recovering from succinylcholine, vecuronium, 0.06–0.08 mg/kg, was given intravenously and ventilation controlled with a volume-cycled ventilator to maintain end-tidal carbon dioxide at 33 ± 2 mm Hg. Anesthesia was maintained with isoflurane, 1.01 ± 0.25%, in 50% nitrous oxide and oxygen. The patients, strapped on the lithotripsy chair, were immersed in the bath to the level of their clavicles with water at 37°C. After immersion the position of the lithotripter chair and the patient's posture were adjusted via a computer-assisted remote control panel to focus the high power shock waves on the targeted stone as seen on the image intensifier screen. Each electrode in the lithotripter's capacitor delivers 700–800 shocks; after a first round of treatment the electrode was replaced to deliver a second round of treatment. The time needed to change electrodes and begin the second series of shocks averaged 6–8 min.

Systemic arterial pressure was measured by a noninvasive blood pressure monitor (Accutorr II Datascope Corp., Paramus, NJ) every 2.5 min, body temperature was monitored by an esophageal temperature probe, and end-tidal concentrations of carbon dioxide, oxygen, isoflurane, and nitrous oxide were measured via a mass spectrometer (Perkin-Elmer, Pompona, CA). A transesophageal ultrasonic Doppler probe

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Table 1. Clinical Details of Patients

Number of patients	11
Age (yr)	53 ± 15
Weight (kg)	79 ± 21
Height (cm)	156 ± 7
End-tidal carbon dioxide (mm Hg)	33 ± 2
Body temperature (°C)	37.2 ± 0.5
Number of delivered shocks for two rounds of treatments	1309 ± 277
Total immersion time in ESWL water bath (min)	44 ± 17

Values are mean ± SD.

(Accucom, Datascope Corp., Paramus, NJ) was inserted into the esophagus to measure cardiac output. The position of the probe was adjusted until an optimal signal echo level was achieved to compute cardiac output.

Although the cardiac output was measured continuously to enable comparisons to be made between subjects, the reported mean ± SD values are those obtained over 3 min during each of the following periods: 1) after immersion in the water bath, immediately prior to shock wave therapy (control); 2) during the last 3 min of the first round of treatment (treatment 1); 3) during the last 3 min of the pause to insert the new electrode (posttreatment 1); 4) during the last 3 min of the second round of treatment (treatment 2); and 5) 10 min after completion of treatment with the patient in the same position and still immersed in water (posttreatment 2). Systemic vascular resistance (SVR) was calculated from mean arterial pressure (MAP) and cardiac output.

After analysis of variance for repeat measurements, a Scheffé test was used to make comparisons between means (8). Differences were considered statistically significant with $P < 0.05$.

Results

Mean arterial pressure was 98 ± 7 mm Hg (mean ± SD) before induction of anesthesia, 76 ± 9 mm Hg after induction of anesthesia, 80 ± 11 mm Hg after immersion in water, and 96 ± 18 and 100 ± 17, respectively, after the first and second rounds of treatment (Table 2). No significant changes in heart rate occurred during the study. Mean cardiac output, 4.8 L/min prior to the first treatment, decreased to 4.1 L/min after the first round of treatment, then gradually increased to 4.7 L/min after treatment 1 before decreasing to 4.3 L/min after the second round of treatment. Systemic vascular resistance increased from a control value of 1461 dyne·sec·cm^{-5} to 1990 dyne·sec·cm^{-5} during the first treatment, decreased to 1620 dyne·sec·cm^{-5} between treatments and increased to 1991 dyne·sec·cm^{-5} during the second round of treatment. Mean arterial pressure, cardiac output, and SVR all returned to control levels within 10 min after completion of the treatment (Table 2). The average total immersion time in the lithotripsy bath was 44 ± 17 (mean ± SD) min and the average total number of shocks delivered during the two treatments was 1309 ± 277 (Table 1).

Analyses of variance for repeat measures showed statistically significant changes in cardiac output, MAP, and SVR. Using the Scheffé test to compare means, both lithotripsy treatments were associated with statistically significant differences between contiguous observations of most variables (Table 2).

Discussion

Extracorporeal shock wave lithotripsy is a noninvasive, relatively safe and effective method for treatment of urinary tract stones. The physical properties and acoustic densities of biologic tissues and solid abdominal organs are similar to water so ultrashort high energy shock waves are able to reach the urinary stone without significant tissue damage. However, Kaude et al. (5), using magnetic resonance imaging (MRI) and radionuclide renal function tests, have shown loss of corticomedullary differentiation, subcapsular hematoma, and partial parenchymal obstruction pattern after ESWL. These findings have been attributed to renal contusion similar to that reported in external mechanical trauma (9). Because of these acute changes, a 3-month follow-up study of patients treated with ESWL has been suggested to determine the reversibility of the renal structural changes (5).

To minimize the risk of initiating cardiac arrhythmias, shock waves are triggered by the R-wave of the ECG and delivered to the kidney during the myocardial refractory period. However, ventricular and supraventricular arrhythmias have been reported during ESWL (10,11). Most of these have been self-limited and did not need treatment, but some required treatment with intravenous lidocaine, and in one patient ESWL was terminated due to persistence of arrhythmia (11).

Anesthesia for ESWL presents a special challenge for the anesthetist: the patient is in a head-up position, respiration must be controlled because the patient is paralyzed, the patient is immersed in water, and high energy shock waves may affect the cardiovascular system and the kidney (5,12). Although the head-up position during anesthesia can be associated with hypotension, peripheral pooling of blood and diminished venous return to the heart are decreased

Table 2. Hemodynamic Responses to Extracorporeal Shock Wave Lithotripsy

Period	Heart Rate (beats/min)	Mean arterial pressure (mm Hg)	Cardiac output (L/min)	Systemic vascular resistance (dyne-sec-cm^{-5})
Control	89 ± 7	80 ± 11	4.80 ± 1.05	1461 ± 372
Treatment 1	90 ± 11	96 ± 18[a]	4.11 ± 1.25[a]	1990 ± 547[a]
Posttreatment 1	90 ± 10	89 ± 16	4.71 ± 1.31	1620 ± 524
Treatment 2	89 ± 9	100 ± 17	4.27 ± 1.31[a]	1991 ± 622[a]
Posttreatment 2	91 ± 17	91 ± 8	5.00 ± 1.28	1540 ± 508

[a] Significant difference obtained between contiguous observations ($F < 0.05$).

by immersion in water (6) to the point that cardiac output and blood pressure are unchanged (7). Duvall and Griffith (3), for example, observed a 20% decrease in systolic blood pressure in ten patients given epidural anesthesia for ESWL, but in seven of the ten immersion in water restored blood pressure to normal. Vasopressors and hydration were needed to treat the hypotension in the remaining three. Frank et al. (10) have reported both hypotension and bradycardia with ESWL during general anesthesia. Our patients, however, had neither bradycardia nor dysrhythmias. They received atropine, 0.3–0.4 mg intravenously, to maintain the heart rate over 80/min, and this may have contributed to the absence of bradycardia.

With the Doppler technique, cardiac output is computed from the product of the heart rate and stroke volume. The stroke volume is calculated from the product of aortic cross section, and flow velocity integral (FVI). The FVI itself is calculated from the product of aortic peak flow velocity (determined from Doppler shift) and half of ejection time during systolic period (13). Our inherent assumptions in measuring cardiac output by this technique were: 1) the absence of aortic valve disease, 2) a smooth round aortic cross section, 3) a negligible change in the diameter of the aorta during the cardiac cycle, and 4) minimal interaction between the lithotripter high frequency shock wave and ultrasound transducer. The Doppler echocardiographic determination of cardiac output correlates well with cardiac output measured by the thermodilution method (14–16).

Cardiac arrhythmias, myocardial ischemia and infarction, cerebrovascular accidents, and renal subcapsular hematoma and demarcation of the corticomedullary region have been reported after ESWL (12), suggesting cardiovascular stress responses to ESWL. Our study demonstrated a reduction in cardiac output together with an increase in MAP and SVR, all of which can be detrimental to patients with cardiovascular disease.

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Congenital Long QT Syndrome:

Changes in QT Interval during Anesthesia with Thiopental, Vecuronium, Fentanyl, and Isoflurane

Niall C. T. Wilton, MRCP, FFARCS, and Charles B. Hantler, MD

Congenital long QT syndrome (LQTS) is a rare abnormality that can present at a young age with syncopal attacks (resulting from ventricular arrhythmias) or sudden death (1). It is thought that LQTS results from an asymmetrical adrenergic stimulus to the heart, which leads to delayed repolarization of the ventricle (manifested by a prolonged QT interval), lowering of the threshold for ventricular fibrillation, an increase in the duration of the vulnerable phase, and an increase in ventricular excitability (2). Untreated, these patients have a mortality of 70%, but treatment with beta-blockers shortens the QT interval and greatly decreases the mortality (1). There are 11 case reports describing the anesthetic management of these patients but only in two (3,4) were any measurements of the QT interval made perioperatively. Changes in the QT interval associated with surgery and anesthesia in patients with LQTS remain undocumented (5). This report documents the effect of thiopental, vecuronium, fentanyl, and isoflurane on the QT interval in a patient with LQTS during an uneventful anesthetic, in whom previous therapy with propranolol failed to shorten the QT interval.

Case Report

A 37-yr-old woman with known LQTS was scheduled for an elective abdominal hysterectomy. The diagnosis of LQTS had been made 10 yr previously when the patient suffered a cardiac arrest at home, was admitted to the hospital in ventricular fibrillation, and was successfully resuscitated. After a thorough workup (including cardiac catheterization that revealed normal coronary arteries), the patient was diagnosed as having LQTS on the basis of a QT interval corrected for heart rate (QTc) of 0.47 sec (the normal QTc $<$ 0.44 sec). A left stellate ganglion block performed at the time of diagnosis failed to shorten the QT interval and the patient was started on propranolol, 20 mg four times a day, which she has taken since that time. Since the diagnosis, the patient has remained asymptomatic. Serial ECGs during the intervening years showed a QTc of 0.47–0.54 sec despite continuing propranolol therapy. The patient was not deaf, nor was there any family history of deafness or sudden death. There was no other relevant medical history, the serum electrolyte levels were normal (specifically calcium and potassium, which are known to alter the QT interval), and the patient was taking no other medications.

On admission, examination showed a healthy patient who weighed 53 kg. The patient was clinically euthyroid. Blood pressure was 100/60 mm Hg, the heart rate was 53 beats/min, the rhythm regular. Auscultation of the precordium revealed normal heart sounds, with no added sounds. A standard 12-lead ECG showed sinus bradycardia with a rate of 53 beats/min and a QT interval of 0.48 sec (QTc = 0.47 sec). Preoperatively, the patient was given her normal morning dose of propranolol and was not premedicated, although 2.5 mg of diazepam was given intravenously for sedation while baseline measurements were made. Prior to and during the operation, two ECG leads selected for the best determination of the T-waves (leads II and V5) were monitored continuously. Measurement of the QT interval was made at intervals from strip chart recorders running at a speed of 50 mm/sec. For each reading, lead II was used as the end of the T-wave was most easily measured from this lead. Five successive RR intervals and QT intervals were determined, then averaged and the QTc derived from the formula of Bazett (6):

$$\mathrm{QTc} = \frac{\mathrm{QTi}}{\sqrt{\mathrm{RR}}}\ \mathrm{sec}$$

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Table 1. Changes in QT Interval during Anesthesia

Events (see text)	Time from induction (min)	QTI (secs)	R-R interval (secs)	Heart rate (beats/min)	QTc (secs)	Systolic/ diastolic blood pressure (mm Hg)
A	−1	0.49	1.00	60	0.49	100/60
Thiopental						
B	1	0.45	0.86	70	0.49	
C	2	0.47	0.89	67	0.50	95/55
Vecuronium + 66% N_2O						
D	3	0.48	0.94	64	0.50	100/60
E	7	0.47	0.96	63	0.48	110/70
Isoflurane 3%						
F	9	0.46	0.92	65	0.48	100/60
G	13	0.41	0.91	66	0.43	100/60
Intubation						
H	14	0.42	0.80	75	0.47	100/70
Isoflurane 1%						
I	19	0.42	0.80	75	0.47	
Fentanyl						
J	20	0.43	1.01	59	0.43	95/60
K	23	0.45	1.01	59	0.45	
L	50	0.42	0.78	77	0.48	110/65
M	120	0.46	0.92	65	0.48	120/60
N	158	0.46	0.88	68	0.49	120/70
Glycopyrrolate/neostigmine						
O	159	0.45	0.79	76	0.51	
P	162	0.43	0.80	75	0.48	130/80
Q	165	0.42	0.78	77	0.48	

Each measurement was given a letter related to its timing during the anesthetic.

The first QTc measurement (A) was made immediately before induction of anesthesia with 250 mg thiopental, with additional measurements being made 1 min (B) and 2 min (C) thereafter while the patient was breathing 100% oxygen. After measurement (C), 6 mg vecuronium was administered and the patient ventilated with 33% oxygen and 66% nitrous oxide. Further measurements of QTc were made 1 min (D) and 4 min (E) after vecuronium. Isoflurane, 3%, was then added and the patient ventilated by mask. QTc was again measured 1 min (F) and 5 min (G) later. Tracheal intubation was uneventfully performed and the isoflurane concentration reduced to 1% with a further measurement (H) made. After 5 min, 250 μg of fentanyl was given and QTc measured immediately before (I) and 1 min (J) and 3 min (K) afterwards. Two additional measurements were made 50 min (L) and 120 min (M) after induction at a time when the concentration of isoflurane in the inspired air was maintained at 1%. At 150 min after induction of anesthesia, isoflurane was discontinued, and 3 min later, the nitrous oxide was discontinued. Glycopyrrolate, 0.6 mg, and neostigmine, 2.5 mg, were given to reverse the neuromuscular blockade and 6 min later the patient was extubated. Measurements of QTc were made before (N), at 1 min (O) and 3 min (P) after reversal, and 1 min (Q) after extubation. The patient was visited 24 hr postoperatively and a final set of QTc measurements made.

Results

The heart rate, QTi, RR interval, and QTc are shown in Table 1, with the letters corresponding to events in the case report. No dysrhythmias occurred during the operative procedure. Twenty-four hours after surgery, the patient was in sinus rhythm with a heart rate of 70 beats/min and a QTc of 0.48 sec.

Discussion

Patients with LQTS are at risk of syncopal attacks and sudden death from ventricular dysrhythmias. These attacks may be triggered by events that cause increased sympathetic activity (1). Successful anesthetic management thus seems to include avoidance of drugs or events that either sensitize the myocardium to catecholamines or increase sympathetic activity and of drugs that prolong the QT interval.

In the preoperative preparation, it is important that the patient continue to receive any beta-blocker therapy as it is this therapy that has been associated with the most effective reduction in mortality from this condition (1). Although propranolol therapy did not shorten the QT interval in this patient, it may still exert a beneficial effect by blocking sympathetic activity and increasing the threshold for ventricular fibrillation (7).

Thiopental, the agent often used for induction of anesthesia, prolongs the QT interval slightly in normal patients about 90 sec after injection (8), but its effect in patients with LQTS is not known. In our patient, the QTc, which was already prolonged, remained essentially unchanged for the first 2 min after thiopental injection.

In considering neuromuscular blockade, it was decided to avoid use of succinylcholine since in normal patients it greatly increases the QT interval (8). Use of succinylcholine in patients with LQTS has been devoid of adverse side effects (9,10), but it has also been associated with ventricular fibrillation (4,11). Pancuronium has been used to provide muscle relaxation in patients with LQTS without problems (9,12) despite its sympathomimetic activity. A recent review of the congenital QT syndrome (5) states that pancuronium is associated with ventricular fibrillation, but review of the case reports to date does not substantiate this fact. It was, nevertheless, decided to use vecuronium in this patient because, although structurally related to pancuronium in clinically used doses, it does not cause sympathetic stimulation (13). Vecuronium in our patient was associated with a slight decrease in the QTc from 0.50 to 0.48 sec 4 min after injection.

Isoflurane has been used in two patients with the LQTS without adverse effects. In one patient, fentanyl was administered before isoflurane and the addition of isoflurane shortened the QT interval but did not return it to the normal range (4). In the other patient, the QT interval was not measured during anesthesia (10). In our patient, 3% isoflurane decreased the QTc from 0.48 to 0.43 sec after 4 min, an effect that was reversed during laryngoscopy and intubation. Isoflurane has a further potential beneficial effect in that it has been shown to increase the threshold for ventricular arrhythmias in response to exogenously administered epinephrine (14).

Halothane has been used in two patients with LQTS (15,16), one of whom developed ventricular fibrillation during anesthesia (15). Enflurane has also been used in two patients with LQTS without adverse effects (17,18).

Fentanyl at a dose of 5 μg/kg was associated with a decrease in QTc from 0.47 to 0.43 sec 1 min later and 3 min later it was 0.45 second, suggesting that fentanyl may be useful in patients with LQTS. The QTc returned to a baseline value of 0.48 secs with the onset of surgery, and remained at this level throughout the surgery.

Reversal of neuromuscular blockade with 0.6 mg of glycopyrrolate and 2.5 mg neostigmine was accompanied in our patient by a temporary increase in the QTc to 0.51 sec 1 min after injection, but by 3 min the QTc had returned to the previous value of 0.48 secs. Extubation did not affect the QTc.

This report suggests that thiopental, vecuronium, isoflurane, and fentanyl are safe drugs in patients with LQTS and reconfirms the beneficial effects and safety of isoflurane in patients with this syndrome. Isoflurane and fentanyl may both have temporary beneficial effects on the QTc when it is prolonged in LQTS but this appears to be overcome by the stimulation of intubation and surgery.

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Osmolalities of Commercially Supplied Drugs Often Used in Anesthesia

Herwig Bretschneider, MD

In a recent study, Furuya and Okumura described hemolysis after administration of high-dose fentanyl (1). In a study of the effects of fentanyl on respiratory patterns in dogs (2), we used doses up to 167.5 μg/kg and found that hemolysis occurred regularly 5 min after total doses of 27.5 μg/kg or more. In looking for a reason, we found the osmolality of fentanyl to be nearly 0 mOsm/kg water, i.e., the same as distilled water.

It is well known that a solution of 0.4% NaCl, which has an osmolality of about 130 mOsm/kg water (3), causes hemolysis. Thus, all drugs with a similar or a lower osmolality will do the same, the amount of hemolysis depending on the volume administered. Because there seems to be a general lack of information about the osmolalities of commercially supplied solutions, by means of a Knauer-Osmometer scaled up to 1600 mOsm/kg water we determined the osmolalities of some drugs we administer in daily practice. Drugs with an osmolality above 1600 mOsm/kg water were diluted 1:10 with distilled water and the result multiplied by 10. Discrepancies between measured and theoretic freezing point depression (osmotic coefficients) were disregarded. The different methods of correcting for the supercooling error and the rationale for the technique used in modern osmometry are discussed elsewhere (4).

Looking at the results (Table 1), the osmolalities of drugs often used in anesthesia ranged between 0 (fentanyl) and 10,800 mOsm/kg water (phenobarbital). Six of the 65 drugs measured showed an osmolality below 130 mOsm/kg water, 42 between 130 and 400, 6 between 401 and 1000, 8 between 1001 and 5000, 2 between 5001 and 10,000, and 1 had an osmolality of more than 10,000 mOsm/kg water.

There seems to be no pharmacologic reason why the osmolality of commercially supplied solutions of

Table 1. Osmolalities of Drugs Used in Our Department in mOsm/kg H_2O Disregarding Osmotic Coefficient

Drug	Osmolality (mOsm/kg water)
Alfentanil, 0.5 mg/ml	291
Atropine, 0.5 mg/ml	298
Bupivacaine, 5 mg/ml	278
Bupivacaine, 5 mg/ml in 8% glucose	478
Buprenorphine, 0.3 mg/ml	297
Calcium gluconate, 10%	276
$CaCl_2$, 10%	1765
Clonidine, 0.15 mg/ml	276
Dantrolene, 1 mg/3 ml in 5% mannitol	300
Dexamethasone, 4 mg/ml	255
Diazepam, 5 mg/ml "Valium Roche"	7775
Diazepam, 5 mg/ml "Valium MM Roche"	243
Diazepam, 5 mg/ml "Diazemuls" (Kabi)	349
Diazoxide, 15 mg/ml	130
Dobutamine, 5 mg/ml	361
Dopamine, 10 mg/ml	277
Droperidol, 2.5 mg/ml	16
Epinephrine, 1 mg/ml	348
Etomidate, 2 mg/ml	4965
Fentanyl, 0.05 mg/ml	0
Flunitrazepam, 2 mg/ml	7240
Furosemide, 10 mg/ml	291
Hexobarbital, 100 mg/ml	745
Ketamine, 10 mg/ml	300
Ketamine, 50 mg/ml	387
KCl, 7.45%	1895
Levallorphan, 1 mg/ml	289
Lidocaine; lignocaine, 10 mg/ml	296
Lidocaine; lignocaine, 20 mg/ml	352
Lidocaine, 50 mg/ml in 7.5% glucose	837
Mannitol, 20%	1260
Meperidine; pethidine, 50 mg/ml	302
Mepivacaine, 20 mg/ml	373
Metoclopramide, 5 mg/ml	280
Midazolam, 5 mg/ml	215
Morphine HCl, 10 mg/ml	54
NaCl, 0.9%	291
$NaHCO_3$, 4.2%	815
$NaHCO_3$, 6%	1095

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Table 1. (*continued*)

Drug	Osmolality (mOsm/kg water)
$NaHCO_3$, 8.4%	1815
Naloxone, 0.4 mg/ml	301
Sodium Nitroprusside,	290
Neostigmine, 0.5 mg/ml	251
Nifedipine, 0.1 mg/kg	3060
Nitroglycerin, 1 mg/ml	281
Norepinephrine, 1 mg/ml	319
Pancuronium, BR 2 mg/ml	338
Pentazocine, 30 mg/ml	307
Pethidine; meperidine, 50 mg/ml	302
Phenobarbital, 200 mg/ml	10,800
Phenytoin, 50 mg/ml	3035
Physostigmine, 0.4 mg/ml	22
Pindolol, 0.2 mg/ml	258
Prednisolone, 125 mg/ml	247
Promethazine, 25 mg/ml	291
Propranolol, 1 mg/ml	12
Ranitidine, 10 mg/ml	59
Scopolamine, 0.5 mg/ml	303
Spironolactone, 20 mg/ml	358
Succinylcholine; suxamethonium, 50 mg/ml	409
Theophylline, 24 mg/ml	134
Thiopental, 25 mg/ml	215
Thiopental, 100 mg/ml	942
d-Tubocurarine, 3 mg/ml	296
Vecuronium, 4 mg/ml	292
Verapamil, 2.5 mg/ml	290

fentanyl is 0. It is possible to change the osmolalities of commercial drug preparations. Diazepam, 10 mg, for example, has widely different osmolalities: Valium Roche = 7775 mOsm/kg water; Valium MM Roche = 243 mOsm/kg water; and Diazemuls = 349 mOsm/kg water.

Apparently none of the investigators who have used high (2,5) and even massive (6) doses of fentanyl have been aware of the low osmolality of fentanyl solutions. Dogs given fentanyl up to total doses of 167.5 μg/kg have survived (2,5). But with doses up to 10 mg/kg (i.e., 200 ml/kg, which is about twice the dog's blood volume), as used by De Castro et al. (6), the dogs did not survive. Toxicologic effects, including sympathomimetic stimulation and convulsions, etc., which the authors attributed to massive-dose fentanyl, were due rather to the massive amount of almost pure water than to the drug itself. These effects can be explained on the basis of cellular hypoxia caused by the strong hemolysis, and/or cellular edema caused by the decrease in plasma osmolality.

In evaluating the data in Table 1, it should be borne in mind that the data, based on drugs supplied to our institution, may not apply to the same drugs supplied to all institutions. The osmolality of commercially supplied solutions of drugs varies from manufacturer to manufacturer.

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ANESTH ANALG
1987;66:363–6

A Retrospective Analysis of Failed Spinal Anesthetic Attempts in a Community Hospital

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Since the introduction of spinal anesthesia more than 85 years ago, there have been numerous periods of enthusiasm and condemnation associated with ever changing attitudes to and concepts of spinal anesthesia (1). With increased understanding of the physiology and pharmacology of spinal anesthesia, it is now established as one of the most useful forms of anesthesia, providing excellent analgesia and relaxation, with documented safety and relative ease of administration. However, Levy et al. (2) recently reported a 17% incidence of failure of spinal anesthetics in a university teaching hospital. Clinical reports describing inability to induce spinal anesthesia, the incidence of inadequate spinal anesthesia and factors associated with spinal failure are limited. The purpose of this retrospective study was to determine the incidence and factors associated with failed spinal anesthetics as seen in a community hospital.

Methods and Materials

A total of 329 consecutive spinal anesthesia performed during a 3-yr period (October 1982–September 1985) by a group of anesthesiologists and anesthetists at Lourdes Hospital were studied. Data on age, sex, height, weight, body mass index (BMI), physical status, and medical problem(s) such as arthritis, spine abnormalities, back pain, previous laminectomy, or fusion were recorded. Variables involved in subarachnoid puncture were also studied, including patient's position (lateral or sitting), needle gauge, number of attempts at dural puncture, paresthesias, free flow of cerebrospinal fluid (CSF), and blood staining of CSF. Other variables studied were anesthetic agent, dosage, addition of epinephrine or phenylephrine, duration of surgical procedure, intraoperative complications, and supplemental drugs used.

A spinal anesthesia was considered successful if it required no supplementation with inhalational anesthetics or parenteral analgesics. If a patient had more than one spinal anesthesia, data from only the first were included in the study.

The means of successful and failed spinal anesthesia groups were compared with independent group tests. The proportions of patients in subgroups in the success and failure groups were compared with χ^2 tests of independence or Fisher's exact tests of proportions, as appropriate. Differences were considered statistically significant if P values were less than 0.05.

Results

Patient Characteristics

Spinal anesthesia was successful in 318 of 329 patients (97%) and failed in 11 patients (3%) (Table 1). The successful and failed spinal groups did not differ significantly with respect to sex, age, height, weight, body mass index (BMI), and obesity (body mass index ≥ 30). However, patients with successful spinal anesthesia differed significantly from patients with failed spinal anesthesias with respect to physical status. In the 318 patients with successful spinal anesthesia, 52 (16%) fell into ASA categories I or II, 152 (48%) were in category III, and 114 (36%) in category IV. All of the 11 patients in whom spinal anesthesia failed fell into category III (100%).

The success and failure groups did not differ significantly in terms of mean duration of surgery. Mean duration of surgery was 80 min in the success group and 119 min in the failure group. The frequencies of different types of surgical procedures ranged from

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Table 1. Patient Characteristics

	Successful spinal anesthesias	Failed spinal anesthesias
Number of patients (total 329)	318	11
Male	222	8
Female	96	3
Age (yr)[a]	70 ± 0.8 (14–97)	66 ± 5.4 (34–86)
Height (cm)[a]	172 ± 0.6 (124–198)	172 ± 3.8 (150–188)
Weight (kg)[a]	71 ± 1.0 (33–147)	69 ± 5.1 (39–100)
Body mass index[a]	24 ± 0.3 (13–54)	23 ± 1.7 (17–37)
Patients with BMI ≥ 30	28	1
Physical status:		
ASA I	18	0
ASA II	34	0
ASA III	152	11
ASA IV	114	0

[a]Values are mean ± SEM, range in parentheses.

Table 2. Technical Factors

	Successful spinal anesthesias	Failed spinal anesthesias	Totals
Position			
Lateral	280	11	291
Sitting	4	0	4
No documentation	34	0	34
Needle size			
22 gauge	303	11	314
25 gauge	15	0	15
No documentation	0	0	0
Number of attempts			
≤3	191	8	199
>3	40	3	43
No documentation	87	0	87
CSF flow			
Free flow	304	11	315
No free flow	1	0	1
No documentation	13	0	13
Blood in CSF			
Blood stained	13	1	14
Clear	277	10	287
No documentation	28	0	28
Agent			
Lidocaine (total)	242	4	246
Alone	70	2	72
With epinephrine	10	0	10
With phenylephrine	162	2	164
Tetracaine (total)	76	7	83
Alone	38	2	40
With epinephrine	10	3	13
With phenylephrine	28	2	30
Dose (mg) (mean ± SEM)			
Lidocaine	85 ± 0.9	83 ± 6.0	
Tetracaine	10 ± 0.2	9 ± 0.4	

one appendectomy to 103 transurethral resections of the prostate.

Technical Factors

In the majority (291 of 294 = 99%) of patients spinal anesthesia was induced in the lateral position (Table 2). In the successful spinal group, 280 (99%) received the anesthetic in the lateral position, 4 (1%) in the sitting position. In the failed spinal group, 11 (100%) were in the lateral position. Position was not a significant factor governing success or failure.

The two groups also were not significantly different in terms of the size of the needle employed. In the success group, a 22-gauge needle was used in 303 patients (95%), and a 25-gauge needle was used in 15 patients (5%). In the failure group, a 22-gauge needle was used in all 11 patients (100%). The groups were also not significantly different in terms of number of puncture attempts. Forty patients (17%) in the success group required more than three attempts; in the failure group, three (27%) required more than three attempts.

Nearly all patients for whom data were available (315 of 316 = 100%) had a free flow of cerebrospinal fluid (CSF). The one patient who did not have a free flow of CSF was in the success group. Blood was in the CSF of 13 patients (4%) in the success group and was in the CSF in only one patient (9%) in the failure group. These proportions were not significantly different.

Paresthesias were recorded in two of the 234 (1%) patients in whom data was available. Nausea was recorded in 12 of 276 patients (4%), and vomiting in five of 274 patients (2%). The drugs most commonly used intraoperatively were diazepam, fentanyl and ephedrine.

Seventy-five percent of patients (246 of 329) had lidocaine spinal anesthesia with or without epinephrine or phenylephrine. Eighty-three of the 329 patients (25%) had tetracaine spinal anesthesia with or without epinephrine or phenylephrine. Lidocaine spinal anesthesias were significantly more successful (242 of 246 = 98%) than were tetracaine spinal anesthesias (76 of 83 = 92%). Of the patients given lidocaine, success was not significantly related to whether lidocaine alone, lidocaine with epinephrine, or lidocaine with phenylephrine was used. However, with tetracaine, the frequency of successful spinal anesthesias did differ significantly between those given tetracaine alone (38 of 40 = 95%), tetracaine with phenylephrine (28 of 30 = 93%), and tetracaine with epinephrine (10 of 13 = 77%). Patients given tetracaine with epinephrine had significantly fewer successful spinal anesthesias than those given tetracaine with phenylephrine. Success or failure were not significantly related to mean dosages of lidocaine or tetracaine administered.

Correlating Factors with Spinal Anesthesia Failure

Seventy-five percent of spinal anesthesias administered involved use of lidocaine whereas tetracaine was used in only 25% of cases. However, 64% of failures were in the tetracaine group (7/11) and 36% were in the lidocaine group (4/11) (Table 2). Hence, the incidence of failures was 1.6% (4/246) in the lidocaine group and 8.4% (7/83) in the tetracaine group. Addition of epinephrine or phenylephrine had no significant influence on success rate in the lidocaine group, whereas epinephrine increased the failure rate and phenylephrine had no effect in the tetracaine group.

Discussion

General anesthesia is the most commonly used technique for most surgical procedures in the United States, even though the popularity of regional anesthesia has been increasing in recent years. This is especially true in community hospitals with the pressures of private practice. In addition, wide acceptance of regional anesthesia may be limited by the time required to administer regional anesthesia, unsatisfactory anesthesia in the hands of the inexperienced, patient's fears based on anecdotal stories, the possibility of multiple attempts, lumbar puncture, and the failure rate associated with regional anesthesia.

Although there are few studies describing the failure of spinal anesthesia, there is only the study by Levy et al. (2), that specifically examines the incidence of failure and associated factors. Failure rate of spinal anesthesias has been reported from 0.46% to as high as 35% (2–5).

In four separate studies, variable failure rates of 0.46% (3), 16% (4), 17% (2), and 35% (5) were reported. Definition of failure of spinal anesthesia is rarely agreed upon. In the study (3) by Moore et al., a spinal anesthesia was a failure only if surgery caused pain whereas Levy et al. (2) considered as a failure a spinal anesthesia requiring general anesthesia any time during a surgical procedure, regardless of the duration of surgery. We used the same criteria as Levy et al. (2). Additional factors such as the use of various types of local anesthetic agents and the types of surgical procedures performed makes comparison of various studies describing failure rates of spinal anesthesias very difficult.

We have used the same criteria as Levy et al. (2) for purposes of direct comparison between a university hospital and a community hospital facing the same limitations including retrospective review of charts, and lack of availability of information on some charts. Despite these limitations, we were able to determine that the failure rate in a community hospital setting is significantly lower than in the university hospital setting described by Levy et al. (3% vs 17%). Our results differ from Levy et al. in that we failed to find any correlation between free flow of CSF and addition of epinephrine and phenylephrine with success or failure of lidocaine spinal anesthetics, while we observed a significantly higher incidence of failure in tetracaine than in lidocaine spinal anesthesias (8.4% vs 1.6%) and in tetracaine with epinephrine than in tetracaine alone (13% vs 5%). In addition, in our study there were no failures due to the duration of surgical procedure extending beyond the duration of spinal anesthesia. In contrast to the report by Levy et al. correlating increased failure with absence of free flow of cerebrospinal fluid, clear free flow was recorded in almost all failed spinals in our study, which may be explained by the fact that we employed 22-gauge needles more frequently than 25-gauge, which in turn may have made detection of flow of cerebrospinal fluid easier due to the larger orifice of the needle. The greater number of failed spinals with addition of epinephrine to tetracaine in our study is also a controversial finding because Levy et al. (2) as well as others (5) reported increased frequency of successful spinals with addition of epinephrine. We do not have any explanation for this surprising finding. Increased incidence of failures seen with tetracaine compared to lidocaine is also interesting, although we do not have an explanation for this finding either.

Even though it is difficult to directly compare the results of this study to those of previous studies, we attribute the high incidence of failure rate in the study by Levy et al. (2) to be possibly peculiar to at least some teaching institutions in which there is inadequate emphasis on regional anesthesia. Similar to the teaching university hospital in the study by Levy et al., general anesthesia was performed in 96% of cases by our group in our community hospital as it is favored by surgeons as well as patients. However, the anesthesia staff at our institution is well versed and favors spinal anesthesia in all appropriate situations. Despite our fairly low failure rate, we believe that further improvement is desirable.

Failure of any type of anesthesia, especially a major conduction anesthesia such as spinal, is frustrating. However, failure has been occasionally encountered by all experienced workers, despite the fact that accepted procedure has apparently been followed (6). In 1907, Alfred E. Barker wrote that "For successful analgesia it is necessary to enter the lumbar dural sac effectually with the point of needle, and to discharge through this, all the contemplated dose of the drug, directly and freely into the cerebrospinal fluid, below the termination of the cord" (6). Failure to follow these details is the most common cause of failure to achieve adequate anesthesia. Other causes of failure include faulty positioning, inadequate dosage, and selection of local anesthetic.

We express our gratitude and thanks to Brenda Hanle and Janice Harris, Director and Assistant Director of Medical Records, for their cooperation and help in providing the charts. We also thank Martha Rust for secretarial help.

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Letters to the Editor

Anesthesia for Magnetic Resonance Imaging

To the Editor:

Magnetic resonance imaging (MRI) has been performed on infants and young children with the use of chloral hydrate, diazepam, fentanyl, or methohexital (1) to produce the quiet immobility needed. Recently, we devised a system for providing endotracheal general anesthesia in infants and children during imaging using a Mapleson D system. Since then, we have used this technique to anesthetize eight children ranging in age from 17 months to 17 yr and ranging in weight from 10.8 to 77 kg. Patients were brought down to a room adjacent to the MRI room, where an anesthetic machine and standard monitoring and suction equipment were located. An IV line was started with the patient awake whenever possible. Otherwise, inhalation anesthesia with nitrous oxide, oxygen, and halothane was started and an IV inserted through which atropine was injected followed by thiopental. Tracheal intubation was accomplished with the use of succinylcholine. A disposable Mapleson D attachment (Product No. 5116W, Vital Signs, Inc., Totowa, NJ) was connected to the endotracheal tube and the patient given 100% oxygen. Once the effect of the muscle relaxant wore off and anesthetic stabilization with further increments of thiopental was established, the patient was disconnected from the anesthetic machine and moved to the MRI room. Oxygen was then delivered to the Mapleson D attachment through several connected plastic tubes, as the oxygen outlet was located about 20 feet away. A member of the anesthesia team monitored the depth of anesthesia throughout the procedure by following respiratory rate and heart rate using an esophageal stethoscope, and by observing the patient for limb movements. Pulse oximetry was used with minimal image degradation provided that the probe lead was long enough to allow the oximeter to be placed as far from the magnet as possible. Small increments of thiopental were given to maintain the depth of anesthesia. Oxygen flow was set at 6–15 L/min, depending on the weight of the patient. Duration of imaging ranged from 90 to 200 min. At the end of the procedure, the patient was transported to the recovery room. All patients except one breathed spontaneously through the Mapleson D attachment. One patient required manual ventilation because of prior excessive sedation. Arterial blood samples in seven of the eight patients revealed Pa_{O_2} values of 413–555 mm Hg, Pa_{CO_2} values of 31–46 mm Hg, and pH values of 7.33–7.44. All patients, except the one who was heavily sedated, were awake within 60 min of arrival in the recovery room.

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Regression Lines Using Multiple Measurements from Multiple Patients

To the Editor:

Using regression lines to illustrate the accuracy of patient oxygenation monitors can be misleading. In their comparison of measurements of transcutaneous oxygen tension (Ptc_{O_2}) and pulse oximetric oxygen saturation (NSa_{O_2}), with arterial oxygen saturation (Pa_{O_2}) and saturation (Sa_{O_2}) determined from radial artery blood samples, Barker et al. (1) lumped together data from many patients to make one regression line. However, the regression lines of individual patients can differ markedly in slope and intercept. Some patients can have correlation coefficients and slopes close to unity; in others there can be particularly poor correlations. Because of individual patient differences it may not even be statistically appropriate to use a single regression line from several patients (2). This was demonstrated in a comparison of transcutaneous with arterial oxygen and carbon dioxide in a group of patients undergoing one-lung anesthesia (3).

This concept is very important for clinicians using, for example, transcutaneous oxygen or pulse oximetry. They must be aware that although the slope comparing trans-

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cutaneous to arterial oxygen may be close to one for a group of patients, there is variation in that slope. Before assuming that a change in a patient's arterial oxygen will necessarily be accompanied by an equal change in transcutaneous oxygen, three or four measurements comparing arterial to transcutaneous oxygen should be made. Because of variability in patients' individual regression lines, a single regression line based on the measurements of a group of patients is not a good indicator of the accuracy of patient oxygenation monitors.

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In Response:

Dr. Lichtor makes an important point regarding the use of regression and correlation in lumped sets of data from many patients. I shall respond separately to his comments on the use of these techniques using $Ptco_2$ and $NSao_2$ data. First, in plotting $Ptco_2$ vs Pao_2, we stated that $Ptco_2$ was not intended as a noninvasive estimate of Pao_2. Therefore, it is improper to use either correlation or regression as evidence that $Ptco_2$ is an "inaccurate" oxygen monitor. The point of interest is that these variables are significantly correlated (just as, for example, F_{IO_2} and Pao_2 are), and that the correlation coefficient and the regression slope depend upon ASA physical status. Performance of regression analysis on individual patients would imply that we were trying to estimate Pao_2 from $Ptco_2$, which was not the case.

Regarding the pooling of data from many patients in analysis of Sao_2 vs $NSao_2$ data, we should remember that the built-in calibration algorithm of the pulse oximeter was generated from pooled data from volunteers (1). Because $NSao_2$ is intended as a noninvasive estimate of Sao_2 for all patients, it is appropriate to analyze pooled data in this manner. We are merely repeating the experiments used to calibrate the device, using patients rather than awake volunteers.

A crucial point made by Altman (2) is that analyses of correlations or regressions can be misleading unless a scattergram of the data is shown. We presented scattergrams for both $Ptco_2$ vs Pao_2 and $NSao_2$ vs Sao_2 in our paper. The correlation and regression results were included for two reasons. First, virtually all method-comparison studies in the medical literature include such analysis. Second, a major point of our paper was to show how these methods had been used previously (3) to reach an erroneous conclusion regarding the "accuracy" of these two monitors. We showed that correlations between these variables are strongly dependent upon the design of the experiment, just as Dr. Lichtor points out in his letter. Conclusions about the value of these monitors cannot be drawn from correlation coefficients. To quote Altman (2), "It is widely believed that 'you can prove anything with statistics,' but it is much more realistic to say that you can establish nothing by statistics alone."

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The Anesthetization of Fanny Longfellow for Childbirth on April 7, 1847

To the Editor:

We are informed in the exhibition "Pain and its Relief" at the National Museum of American History, Smithsonian Institution, and in the relevant catalog by Knight (1) that the first obstetrical anesthesia in the United States occurred when ether was administered to Fanny Longfellow by her husband, Henry Wadsworth Longfellow. This is not the first time this has been alleged. In 1955, Wagenknecht referred to Fanny's courage in inhaling the anesthetic and to Henry's greater courage in administering it (2). The validity of this allegation has, however, not been vigorously evaluated. It was the poet's purported involvement that prompted my search of primary sources of information for verification of what seemed to be a preposterous assertion.

Samuel Longfellow, brother and official biographer of Henry, tersely comments in the biography that the birth of a girl in Craigie House, the estate of Henry and Fanny, was a joy to all. Neither attendants nor anesthesia were mentioned (3).

The prestigious *Boston Medical and Surgical Journal* provided evidence of a physician in the Boston area who was knowledgeable in the administration of ether analgesia. He was Nathan Cooley Keep, MD, who considered dentistry a medical specialty and was named first Dean of Dentistry at Harvard. In an article that had been communicated to the journal on April 3, 1847, and published on April 7, the date of Fanny's delivery, Keep stressed the use of pure ether rather than a commercial product, discussed his anesthetic apparatus and aspects of the physical chemistry of the drug, and stated his observations of its effects based upon his use in at least 200 dental surgical cases (4). The next issue of the same weekly journal contains a classical report of the successful use by Keep of ether analgesia in a case of natural labor which occurred on April 7 (5)! For ethical and probably several other delicate and restraining reasons, he did not reveal the identity of his patient. The following year, Walter Channing, the eminent Boston obstetrician, quoted verbatim the latter of Keep's letters and prefaced it with acknowledgement that its author was the first person to use ether for an obstetrical delivery in America (6).

Dissatisfied with highly suggestive, but only circumstantial evidence of possible involvement of Dr. Keep in Fanny's delivery, I visited Craigie House in Cambridge to peruse journals and letters of Fanny, but found nothing decisive concerning April 7, 1847. Unfortunately, her journal for 1847 was missing from the collection.

The Houghton Library at Harvard University has the largest holdings of memorabilia of Henry Longfellow. There I requested and graciously obtained the holding I most desired—*The Journal of H.W.L., 1847–1848* (7). There, on page 19, is Henry's entry for April 7 and the beginning of that for April 8, 1847. By permission of the Houghton Library I quote page 19 in its entirety:

> Wednesday 7. This morning at twenty minutes past ten was born in the Craigie House a girl, to the great joy of all.
>
> Fanny heroically inhaled the vapor of sulphuric ether, the great nepenthe, and all the pain of labor ceased, though the labor itself went on and seemed accelerated. This is the first trial of ether at such time in this country. It has been completely successful. While under the influence of the vapor, there was no loss of consciousness, but no pain. All ended happily.
>
> Thursday 8. Fast day. Went to town to see Dr. Elliot about my eyes. Stopped in to Dr. Keep's, *the dentist, who administered the ether yesterday, to report favorably* (italics added), and had the stump of a double tooth extracted under the ethereal vapor. On inhaling it, burst into fits of laughter. Then my brain whirled round and I seemed to soar like a lark spirally into the air. I was conscious when he took the tooth out, and cried out as if from infinitely deep caverns 'Stop!' but I could not control my muscles or make any resistance, and out came the tooth without pain.

It is interesting that Samuel Longfellow's biographic account of brother Henry in 1886 contained an almost identical version of the above portion of the entry for April 8 except for the omission of the italicized part of the sentence (3).

Hopefully, this unveiling of an obscure bit of anesthesia history may assist in avoiding future error and restore credit to Nathan Cooley Keep, MD, to whom it belongs, for being the first to use anesthesia for childbirth in the Western Hemisphere.

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External versus Implantable Devices for Chronic Narcotic Infusion Therapy

To the Editor:

I read with interest the report on intraspinal narcotic administration via implantable pump by Waldman et al. (1). Intraspinal narcotic therapy appears to be a viable approach to the management of pain in many terminal cancer patients (2). Suitable delivery devices greatly enhance the feasibility and effectiveness of such therapy. There are several disadvantages inherent in the use of implantable devices, however.

The cost of implantable pumps can be significant, as high as $5000; implanted pumps must be disposed of after use with a single patient. A minor surgical procedure is required for implantation, and complications, including skin breakdown over the implantation site, have been reported in as many as 9% of patients (3). Medication replenishment and changes in infusion regimens are made more difficult by the implantation of infusion devices.

Two devices suited for ambulatory intraspinal narcotic infusion, the CADD-1® and the CADD-PCA® (Parmacia/Deltec, Piscataway, NJ), have recently been introduced commercially. These miniaturized devices are designed for external use; they are not implanted. The devices weigh 450 g and are slightly smaller than a videocassette; they operate with standard 9 volt batteries. A disposable 50-ml drug reservoir is attached to the devices. Holsters are provided for user convenience. The pumps are suited for intravenous or intraspinal therapy. The CADD-PCA is designed for "demand" or "patient-controlled" regimens as well as for continuous infusion. Cost of the devices is $2400–$2900. These externally operant devices have several advantages over implantable systems for chronic ambulatory intraspinal and intravenous narcotic administration.

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"Unapproved" Use of Drugs

To the Editor:

In his review, "The Clinical Use of Premedicants" (Anesth Analg 1986;65:963–74), Dr. Paul F. White's incorrect terminology of hydroxyzine not having received "official approval" from the Food and Drug Administration for intravenous use could be misleading to anesthesiologists.

In this age of overzealous attorneys and pharmacy directors, it is notable that the publishers of the *Physicians' Desk Reference* and the AMA have attempted to resolve this concern and confusion among practitioners (1,2). In addition, the FDA Drug Bulletin states "The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature (3)."

This clarification is important to anesthesiologists, who commonly use drugs for unlabeled uses (curare for defasciculation, lidocaine for modification of the stress response to tracheal intubation, nitroglycerine ointment as a topical venodilator) and in unlabeled routes (rectal methohexital, intravenous methadone, epidural fentanyl).

As there is little financial motivation to apply to the FDA to broaden the indications for a generically available preparation, we should not expect product literature to keep pace with our ever improving therapeutic ability.

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Double Internal Jugular Vein Cannulation in Adult Patients Utilizing a Single Venipuncture

To the Editor:

Fabian et al. have presented a cogent and comprehensive letter outlining the indications, benefits, technique, and efficacy of double internal jugular vein cannulation in adult and pediatric cardiac surgery patients requiring a double venipuncture (Anesth Analg 1986;65:419–20). Although their method is without obvious flaw, we have been performing rapid double internal jugular vein cannulations in adult patients utilizing a single venipuncture with theoretical as well as practical advantages over the technique described by Fabian et al.

After obtaining access to the internal jugular vein via an 18-g over-the-needle catheter, a J-wire (Bard, VSC I Percutaneous Arterial Venous Catheter Introducer Kit, C.R. Bard, Inc., Billerica, MA) is inserted, and the catheter withdrawn. At the site of J-wire entry into the skin, a small incision is made, and an 8F sheath dilator unit with side port/hemostasis valve catheter-to-sheath adapter is passed over the J-wire. The dilator and J-wire are removed, and the 8F sheath is left in place without suture securement to the skin. Two 0.0889-cm diameter straight tip guidewires, obtained from the Bard Percutaneous Arterial Venous Catheter Introducer Kit mentioned above, and the American Edward Multi-Med Catheter Kit (American Edwards Laboratories, Irvine, CA), are advanced through the 8F sheath into the internal jugular vein (Fig. 1). The introducer sheath is carefully withdrawn, while concurrently stabilizing both guidewires (Fig. 2). A purse string suture is fastened around one guidewire, while the 8F sheath dilator unit with side port/hemostasis valve catheter to sheath adapter is readvanced over the second guidewire. The dilator and guidewire are removed and the 8F sheath is suture-secured to the skin (Fig. 3). A pulmonary artery catheter enveloped in a sterile collapsible sleeve is positioned through the 8F sheath in standard fashion. The purse string suture securing the remaining guidewire is released, and a 7F dilator from the triple lumen Multi-Med Catheter Kit is threaded over the guidewire to enlarge the insertion site. After withdrawal of the 7F dilator, the triple lumen Multi-Med catheter is subsequently advanced over the guidewire. If the triple lumen catheter does not pass easily, the puncture site may be enlarged by a scalpel incision. After suture securement of the triple lumen catheter to the skin, a single 3-0 silk mattress suture is placed between the pulmonary artery catheter and triple lumen catheter entry sites. This both apposes skin margins and fully occludes the incisional edges of the wound. Full apposition and occlusion of the incision promotes wound healing and helps avoid unrecognized air entrainment.

One of the advantages for double internal jugular vein cannulation utilizing a single venipuncture is that patient discomfort associated with the procedure is decreased, as

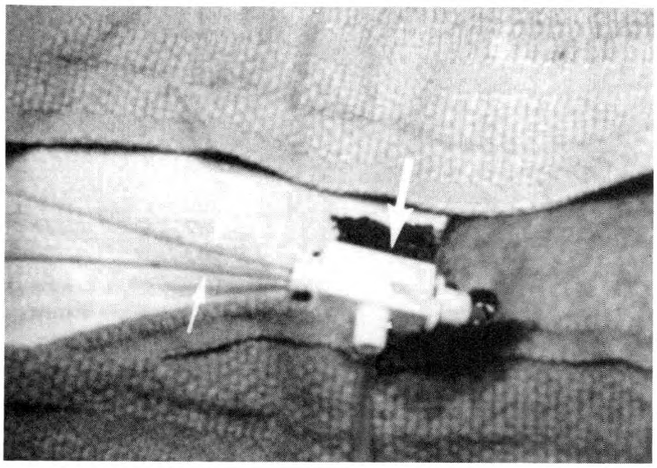

Figure 1. Two 0.0889-cm diameter straight tip guidewires (small white arrows) advanced through the 8F introducer sheath (large white arrow). The clear plastic tube extending from the hub of the introducer sheath serves as a venous access conduit.

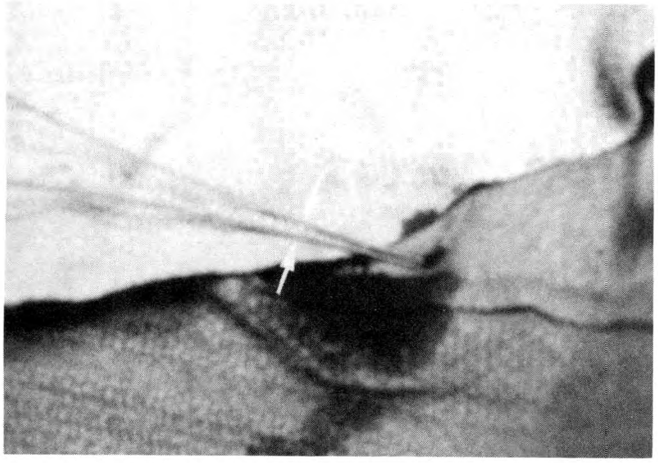

Figure 2. With the 8F introducer removed, two straight tip guidewires remain positioned in the internal jugular vein (small white arrows).

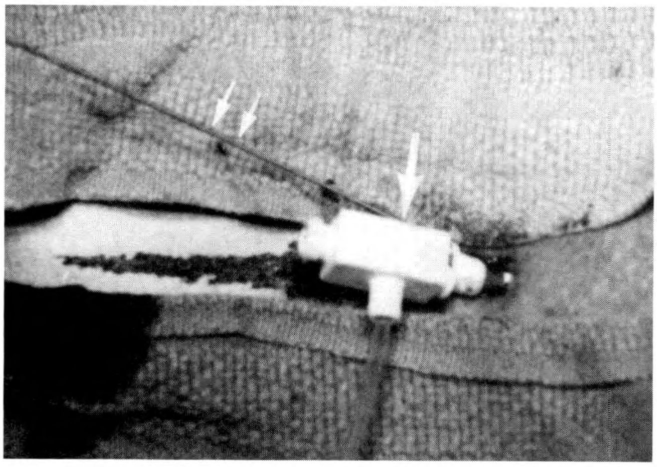

Figure 3. Straight tip guidewire alongside repositioned 8F introducer sheath.

there is no need for two needle punctures. Additionally, a single venipuncture technique minimizes the risk associated with internal jugular vein cannulation, including pneumothorax, carotid artery puncture with local hematoma formation, and failure to localize or successfully insert a second over-the-needle catheter.

Within the past year at our institution, more than 25 adult cardiac surgery patients have undergone this procedure without any known untoward sequellae. Realization of this technique by attending and house staff physicians proficient in cannulating the internal jugular vein adds little time to the standard placement of a pulmonary artery catheter. At the time of removal of both the triple lumen catheter and the 8F sheath with the pulmonary artery catheter, it has been our practice to temporarily apply an occlusive pressure dressing for optimal hemostasis. The 3-0 silk mattress suture initially placed between the triple lumen catheter and the 8F introducer sheath at the time of catheter placement, is temporarily left in place to promote incisional apposition and closure.

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Reference

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Medullary Effects of Local Anesthetics

To the Editor:

In their recent article regarding an alternative mechanism for the cardiotoxic effects of local anesthetics, Thomas et al. raise a timely issue (Anesth Analg 1986;65:444–50). As our knowledge of the importance of the central nervous system as a mediator of cardiovascular responses increases, it is logical to consider whether the cardiovascular toxicity associated with overdosage of local anesthetics could also involve CNS pathways, either as the primary or a contributing mechanism of action. The model of the vasomotor network that is given provides an easily comprehensible summary of the complex neural interactions. The cardiovascular results of chemical and electrical stimulation of the C1 and NTS cell groups correlate well with the model. However, I have some difficulty with the extrapolations regarding the changes observed after local anesthetic administration.

Application of the anesthetics to the C1 region increases cell firing and produces hypotension. Loss of inhibitory inputs combined with blockade of C1 axons as described by the authors provides a reasonable explanation of these observations. However, the hemodynamic responses observed after application of the anesthetics to the NTS seem inconsistent with the given model. Assuming the drug effects are identical to those seen after administration to the C1 region, abolition of excitatory inputs to the NTS combined with blockade of the NTS output would produce a decrease in cell firing as observed but also decrease in the inhibitory input to C1 cells. This should produce an increased activity of the C1 cells with an increase in blood pressure, not the hypotension that was observed.

Does this inconsistency indicate the model for the vasomotor network is incorrect or just incomplete? Could it be possible that the drugs are only selectively blocking certain axons at the concentrations used? Alternatively, are additional fibers of passage also being effected that result in activation or inactivation of additional control networks?

As with most good experiments these studies raise more questions than can be dealt with in a single presentation. In addition to a further explanation of the hemodynamic responses it would be interesting to know a few additional facts to aid the transition to clinical practice. What are the effects of increasing or decreasing the concentrations of the local anesthetics? Perhaps such studies would demonstrate a differential effect on selected pathways. Can similar concentrations of these drugs be obtained in these brain regions after systemic administration of the local anesthetics? Finally, can the same changes in cell firing be observed after systemic administration of the anesthetic?

I look forward to followup studies. If the relative importance of such actions on the central nervous system could be defined, the potential for more rational treatment of toxicity would be an obvious improvement in our current clinical practice.

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In Response:

Dr. Fleming has addressed an excellent point. In our original manuscript, we refrained from speculation with regard to the apparently contradictory hemodynamic responses at NTS. The only pathways presented in Figure 1 of our original manuscript were those which had been established by electrophysiologic and/or histochemical techniques (1). Thus we feel our diagram is incomplete rather than inaccurate.

As noted in our original article, the hypotension and bradycardia seen with the administration of local anesthetics at the spinal cord level and an absence of bradycardia with local anesthetic administration at C1 suggest that there is an efferent fiber projecting from the central nervous system that does not originate from C1 but does influence the heart. This efferent fiber may arise from NTS. Local anesthetic injections at NTS produced significant decreases in mean arterial pressure (MAP) and heart rate (HR). In addition, arrhythmias developed in approximately 50% of the animals. The hypotension and bradycardia seem contrary to that expected from Figure 1 of our original manuscript (1). A blockade at NTS would be expected to produce hypertension and tachycardia. Thus these data also suggest that there is another efferent fiber from NTS to the spinal cord that affects the heart. Because the injections into NTS produced arrhythmias, as did injections into the spinal cord, it can be argued that the spinal cord fibers, when blocked, produced bradycardia via fibers originating from NTS or adjacent to the NTS structure. It has been shown that NTS projects to the cervical spinal cord and that, at C3, there is a sympathetic relay to the heart (2). It is doubtful that the excitatory fiber from NTS would go to IML because it has already been demonstrated that the projection from NTS to IML is inhibitory (3). Also, it is unlikely that NTS would send both an inhibitory and excitatory fiber to IML. Thus the proposed excitatory afferent NTS fiber probably projects to C3 in the spinal cord (Figure 1A). Figure 1A is essentially identical to Figure 1 of our original manuscript with the exception of the incorporation of two new efferents originating at NTS. If our new pathways are correct, several criteria will have to be met. First of all, the excitatory fiber would have to be a tonic efferent fiber because its blockade led to hypotension and bradycardia. Our studies showed that excitation of NTS led to hypotension. With the idea of an excitatory fiber to a sympathetic relay center, one would expect that NTS stimulation would lead to hypertension and tachycardia. It is possible that the tonic excitatory fiber is at its highest activity at rest. Therefore, stimulation of NTS cannot cause further excitation of this fiber. On the other hand, the inhibitory fiber from NTS, which would also be tonically active (but not at its maximum activity at rest), would overcome the excitatory influence from the other NTS projection thus resulting in bradycardia and hypotension. With blockade of NTS, both the excitatory and inhibitory fibers are blocked, but because the excitatory fiber has a greater influence than the inhibitory fiber in a resting state, the heart rate and blood pressure would decrease. The reason NTS might have both types of fibers is because the excitatory fiber would function to maintain resting MAP and HR, while the inhibitory fiber would function to modulate changes in MAP and HR.

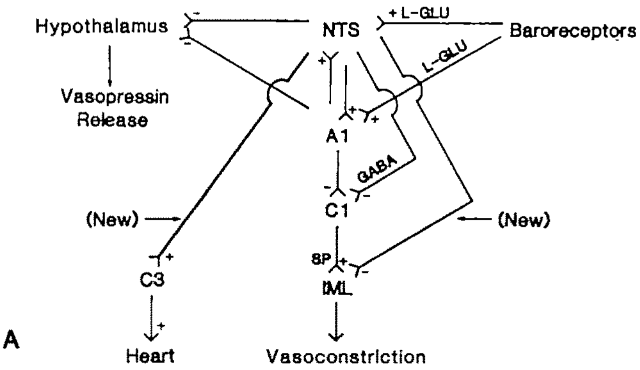

Figure 1A. See response to "Medullary Effects of Local Anesthetics" for explanation.

It should be possible to verify the existence of such fibers using standard histochemical techniques.

As Dr. Fleming pointed out, preliminary studies, such as the case in point, serve to raise far more questions than can be addressed from a single set of experiments. The three major questions raised by Dr. Fleming are in fact currently under investigation. Unfortunately, electrophysiologic studies such as these require meticulous attention to detail as well as vast amounts of *real* time. We do hope to be able to submit data from our followup studies within the next year.

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Intubating by Sense, not Dollars

To the Editor:

At our teaching institution, physician education includes cost containment. Recently, pharmacy administrators circulated among our anesthesia staff and trainees the hospital cost per unit dose of various muscle relaxants (Table 1).

Table 1. Cost of Various Muscle Relaxants[a]

Atracurium	10 mg/ml 10 ml	$23.58
Vecuronium	10 mg	$10.73
Succinylcholine	20 mg/ml 10 ml	39¢
Pancuronium	2 mg/ml 5 ml	$ 7.86
d-Tubocurarine	3 mg/ml 20 ml	$ 5.30
Gallamine	20 mg/ml 10 ml	$ 7.88
Metubine	2 mg/ml 20 ml	$12.66

[a] As of June 1986.

However, what initially appears to be a good method of making anesthesiologists more cost conscious when considering use of new nondepolarizing relaxants is misleading. Table 2 lists depolarizing and nondepolarizing relaxant dosages taken from a standard anesthesia text (1) plus calculation of the actual cost per tracheal intubation for a 70-kg individual. When actual costs per intubation are compared, the differences become less dramatic. With vecuronium and atracurium, characteristics such as intermediate duration, minimal cardiovascular side effects, minimal or no accumulation, and with atracurium an alternate method of metabolism, these agents are advantageous regardless of cost. If these agents are used for short operations, the avoidance of possible prolonged postoperative muscle paralysis will reduce price differences even further (2). Although many anesthesiologists feel the appropriate cost comparison should be made per case rather than per milligram (3), the cost per intubation remains an important consideration.

Table 2. Guide to Muscle Relaxants by Dollars

Drug	Potency factor	Intubation dose (mg/kg)	Dollars (per 70 kg)
Pancuronium	1	0.06–0.08	3.30–4.40
Metocurine	4	0.3–0.4	6.65–8.86
d-Tubocurarine	7	0.5–0.6	3.05–3.71
Gallamine	40	3.0–4.0	8.27–11.04
Atracurium	4	0.4–0.5	6.61–8.26
Vecuronium	0.9	0.07–0.10	5.24–7.49
Succinylcholine	—	1–2	0.14–0.28

Although cost containment in anesthesia has become a necessity, especially in a training program, the choice of muscle relaxants should be based on sound clinical judgement in deciding which relaxant provides maximal patient safety and optimal operating conditions. While others concern themselves with the dollars and cents of intubation, we, as anesthesiologists, should concern ourselves with intubating by sense, not dollars.

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Another Technique for Extending the Life of Oximetry Monitoring Probes

I read with interest the letter by Alpert and Cooke (Anesth Analg 1986;65:826–7) describing a technique for prolonging the life of disposable oximeter monitoring probes. I have been utilizing a different technique for the same purpose.

First, one carefully trims the adhesive tape off the sides of the disposable probe. The probe is then placed on the inner surface of a malleable aluminum finger splint that has

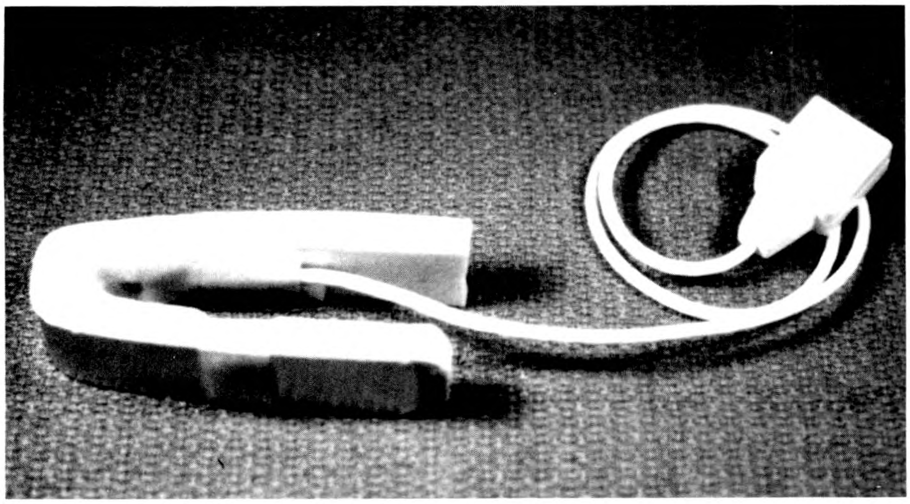

Figure 1. A simple device which allows for repeated uses of disposable oximeter probes.

been bent to accommodate the adult index finger (Fig. 1). The probe is then easily secured by taping it to the finger splint.

The probe device fits snugly on most adult patients and applies quickly and easily. It is lighter than nondisposable probes and applies more securely to the finger. This simple "nondisposable" device allows for repeated uses of "disposable" oximeter probes and is a cost-effective technique for both patients and health care providers.

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Book Reviews

Quantitation, Modelling and Control in Anaesthesia

Horst Stoeckel, ed. Stuttgart: Georg Thieme Verlag, 1985, 310 pp, $50.20.

A group of eminent scientists gathered at the University in Bonn in June 1984 to discuss topics related to the quantitative description of the fate of drugs used in anesthesia. The proceedings of the conference are now published for the benefit of a larger audience, specifically for those anesthesiologists who are interested in modelling and quantitative aspects of anesthesia.

As can be expected, the original contributions by authors from three continents cover a wide range of advanced topics. The development of what is now termed pharmacokinetics was traced by Professor Dengler to the middle of the last century, when Schmiedeberg measured the concentration of chloroform in the blood. Anesthetic drugs and sedatives (e.g., thiopental) continued to play a prominent role in the attempts to correlate the amount of the drug in the body (plasma concentration) with the pharmacologic effects. Improvements in analytical methods, data collection, and measurement of pharmacologic responses opened new horizons and the contributions in these proceedings reflect the current state of the art in pharmacokinetics. The presentations cover the quantitative descriptions of several groups of drugs (opioids, hypnotics, benzodiazepines, muscle relaxants); measurement of pharmacologic responses (EEG and neuromuscular block); correlation between the two; the effects of disease states and age on pharmacokinetics; servocontrolled administration of drugs; and sophisticated models based on physiologic approach, system analysis or population pharmacokinetics. Clearly, this field of research is in a state of rapid development. Some results (e.g., the concept of organ clearance) are relatively simple and will immediately benefit the practicing anesthesiologist, others perhaps only in the future.

The editor included in the text the discussions that followed the presentations. This is welcome, as the discussions convey to the reader the feeling of being present at the conference and reveal interesting differences in opinions among the participants. The presentations of each working day were skillfully summarized by Mather and van Rossum. Unfortunately, the text is marred by many typographical errors, some interfering with the understanding of the text. The contribution by Hull, pointing out the limitations and pitfalls of pharmacokinetic analysis, is especially outstanding.

Although the practicing anesthesiologist may be overwhelmed by the material presented, I recommend the book as a reference for advanced information on the current issues in pharmacokinetics. The material will fascinate, challenge, and even stimulate the research-oriented anesthesiologists.

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Clinical Controversies in Neuroanesthesia and Neurosurgery

J. Matjasko and J. Katz, eds. Orlando, FL: Grune & Stratton, Inc., 1986, 270 pp.

The concept of this text is a useful one. The general format is a presentation of information mixed with controversy, followed by recommendations for practice. The five chapters cover cerebrovascular disease, spinal cord injury, intracranial tumors, head injury, and aneurysms.

Ischemic cerebrovascular disease is examined thoroughly from both the anesthetic and surgical viewpoints. The clear and the controversial indications for carotid surgical procedures are presented with equanimity, and opinions are stated as such. The relationships between degree of carotid stenosis, severity of stroke, hypertension, and indications for carotid endarterectomy are subtly interwoven so as to present a clear picture, but only when this is directly sought in reading. One wonders if this picture will escape the notice of the uninitiated. The most striking positive feature of the chapter is its balanced clinical orientation to controversy, leaving the reader with a reasonable guideline by which to practice.

Cervical spinal cord injury is discussed thoroughly and well. At times clarity and precision are impressive; other small sections are repetitious. For example, three different "grading index" systems are described; although each is useful to certain practitioners, the reader is left with an impression of a tendency to excessive medical classification. The discussion of intubation, always a thorny problem in cord injury, is clear, practical, and reflects the good judgment of the authors. The section on chest physiotherapy is very comprehensive with few repetitions. There was little controversy in this chapter except for the very last paragraph.

The division of the discussion of management of patients with brain tumors into supratentorial and infratentorial allows for greater clarity. The emphasis on ICP monitoring before induction of anesthesia as a near routine in craniotomy patients is an overly compelling mixture of fact and anecdote. Fortunately the authors retreat from a hard line position in the less clear recommendations that an ICP monitor should be placed "if indicated." The statement that volatile anesthetics should not be used with large tumors unless ICP is monitored does get the reader's attention. It probably is not quite fair to characterize Dr. Michenfelder's current opinion on mannitol dose based on quoting his work from 1969. He is capable of changing his opinion based on work done in the ensuing 17 years.

The description of the sitting position on page 159 is misleading, where one death in Gronert's series is attributed to the "head up" position. The head up position described was a prone patient tilted slightly head up, not sitting. Table 3 lists reported cases of paradoxical air embolism (PAE) all of which suffered apparent severe deficit. No mention is made of reports of PAE by transesophageal echocardiography which did not result in apparent deficit. This balance is needed less the reader feel that all PAE produces catastrophic results. On balance this chapter is very good and full of information that clinicians can find very useful in directing their practice.

The management of the patient with severe head injury is clinically relevant, well-documented, and adheres to the format of exploration of controversy followed by recommendations wherever possible. The section on brain death is particularly clear. All anesthesiologists attending organ donors should review these eight pages.

The principles in managing the patient with intracranial aneurysm are reviewed and discussed directly and concisely. Different approaches are clearly presented and recommendations made where the authors deem appropriate. However, it is probably a needlessly depressing overstatement to suggest that "management mortality" has not changed in 40 years. I suspect the anesthesiologist who anesthetized aneurysm patients in 1946 would feel that the management of these cases is very different today.

On balance, this is a very successful text that directly and clearly states neurosurgical and neuroanesthetic controversy, gives adequate documentation for even the in-depth reader, and presents the practitioner with recommendations. If neuroanesthesiologists and neurosurgeons are to communicate, they should be aware of the contents of this text. It should serve as a useful bridge.

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Respiratory Failure

R. R. Kirby and R. W. Taylor, eds. Chicago: Year Book Medical Publishers, 1986, 665 pp, $75.00.

The editors' stated purpose of *Respiratory Failure* is to "attempt to provide the busy clinician with enough information to approach respiratory failure in all age groups knowledgeably." To achieve this goal, the editors enlisted the help of 26 authors to contribute 36 chapters, with surprisingly uniform style. The text is divided into five sections that cover basic physiologic concepts: respiratory failure in the neonate, infant, and child; respiratory failure in the adult; diagnostic techniques; and therapeutic modalities. All of the chapters in this book are well-referenced and include an academic discussion of the literature.

The section on Basic Concepts includes a brief historical perspective on the treatment of respiratory failure in the Critical Care Unit and a philosophic chapter on the practice of respiratory critical care, which emphasizes the need for team effort. Respiratory failure is defined in the chapter on Classification of Respiratory Failure as "impairment in the lungs' ability to maintain adequate oxygen and carbon dioxide homeostasis." Hence, this text covers problems of both oxygenation and ventilation. However, within the text, the term "respiratory failure" is occasionally used to describe failure to oxygenate the arterial blood, occasionally to describe ventilatory failure, and occasionally to describe both. As a result, there are places in the text where the distinction among these three is lost, thereby creating confusion.

The first section concludes with a pulmonary physiology chapter which is lucidly written and gives sufficient detail to render a working knowledge of lung function. This book was of personal benefit as an excellent text from which to study for the ABA Critical Care Examination.

The next section, on Respiratory Failure in the Neonate, Infant, and Child, first discusses the physiology of the fetal transition. Although the text is excellent, it would have been enhanced tremendously by figures.

The third section, Respiratory Failure in the Adult, begins with a chapter that broadly discusses pulmonary edema. The chapter on Adult Respiratory Distress Syndrome is comprehensive and contains 351 references. The chapters relating pulmonary aspiration, chronic obstructive lung disease, asthma, and pulmonary embolism to acute respiratory failure discuss the pathophysiology and therapy of these diseases. A rational approach to postoperative respiratory failure is organized well, but repeats detailed basic physiology which appears earlier in the book. Two chapters devoted to pneumonia and infectious disease are followed by a short summary of cardiac function during respiratory failure and during the application of mechanical ventilation and positive end expiratory pressure.

The section on Diagnostic Techniques discusses the use of three primary modalities: physical examination of the patient, radiology with particular emphasis on the evaluation of pulmonary infiltrates, and fiberoptic bronchoscopy. The academic, well-referenced discussion of the physical examination is a tribute to the skill and art required to gain information from relatively simple observation—a method of data acquisition too easily forgotten. In this section, the fiberoptic bronchoscope is discussed as a diagnostic and therapeutic tool. Additionally, its value in performing tracheal intubation is discussed both here, and in the chapter on Tracheal Intubation. The final section of the book, Therapeutic Modalities, contains ten chapters that include Therapeutic, Supportive, and Monitoring functions. This section also includes a chapter on Complications of Therapy, and an entire chapter devoted to Pulmonary Barotrauma.

In summary, this text book covers in detail the broad spectrum of respiratory failure for all age groups and discusses currently available modes of therapy, support, and monitoring for these disease processes. The index is comprehensive. This is an excellent textbook which can be used by the student of Critical Care Medicine, the practicing clinician, or those seeking a comprehensive review.

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Current Concepts in Transfusion Therapy

George Garratty, ed. Arlington, VA: American Association of Blood Banks, 1985, 323 pp, $34.00.

In spite of its title, this publication of the prolific American Association of Blood Banks is not likely to be of much help for the average anesthesiologist seeking a reference on transfusion therapy. The chapter on platelet concentrates deals primarily with preparation and storage. A chapter on therapy for coagulation disorders is more clinically oriented, timely, and complete, including information on subjects such as DDAVP, antithrombin III concentrates, protein C, and heat-treated concentrates. Fresh frozen plasma is well covered in its own chapter by Harold Oberman. He explains much of the factual basis behind the 1984 NIH Consensus Conference on Fresh Frozen Plasma. The other five of this book's eight chapters stress granulocyte therapy and immunology, and as such are not closely related to anesthesiology. Another AABB 1985 publication, *The 9th Edition of the Technical Manual* (Widmann F, ed., Arlington, VA: AABB, 1985, 515 pages) would be recommended for those seeking a more complete reference on current transfusion therapy.

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Anesthesia for Eye, Ear, Nose and Throat Surgery

J. D. Morrison, R. K. Mirakhur, and H. J. L. Craig. New York: Churchill-Livingstone, 1985, 207 pp, $37.50.

Although presented as a second edition, this is essentially a new book, thoroughly rewritten and updated. The inconsistent quality of the first edition (1975) has been corrected by limiting the contributors to three capable authors. The book is balanced 60% ENT and 40% Eye, and is generally organized by anatomy and specific surgical procedures. The ample current references (mainly from the UK) at the end of each chapter serve as a good introduction to the literature for the uninitiated. The index section is thorough and useful.

The style is chatty and verbose but is easily read. The emphasis is on clinically oriented, practical advice for a wide variety of clinical case situations based on clinical experience and supported by the literature. The authors are to be commended for their attention to appropriate anatomy lessons in both ENT and Eye sections. The two introductory chapters on Eye anatomy and physiology and factors affecting intraocular pressure are excellent reviews. The discussion of systemic effects of eye medications and the interaction of nitrous oxide and sulfur hexafluoride gas are important and not often found in texts.

Although the controversy about oculocardiac reflex prevention and treatment was well-presented, there could have been a more balanced discussion of the use of muscle relaxants in open eye-full stomach situations, incorporating Libonati's clinical experience with succinylcholine, the problems of large dose pancuronium, and noting the limitations of vecuronium and atracurium in rapid sequence intubations.

There are gaps in content coverage. The next edition should include discussion of compromised airways, difficult intubations, fiberoptics, techniques of topical laryngeal block for awake laryngoscopy, thyroid surgery, retrolental fibroplasia, congenital syndromes often found in eye patients and out patient anesthesia for EENT surgery. The section on laser surgery could be expanded.

In summary, I give this book an A for being current, B+ for organization, B for style, and a B for content. I recommend this book as a solid, quick introduction to the literature and vagaries of anesthetic management for Eye, Ear, Nose, and Throat Surgery.

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Addendum to 1987 Abstracts

The following abstract was inadvertently omitted from the supplement of abstracts presented at the International Anesthesia Research Society 60th Congress, published in February 1987:

> Colavita RD, Pelligrino DA, Miletich DJ, Albrecht RF. Beagle puppy model of the neonatal brain: effect of halothane on somatosensory evoked potentials. 1987;66:S191A.

The authors are from the Department of Anesthesiology, Michael Reese Hospital and Medical Center, Chicago, IL 60616.

A Guide for Authors

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Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of the articles not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766–71 and *Lancet* 1982;284:1766–70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in minors, by parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.

☐ Technical communications are papers that deal with instrumentation and analytic techniques.

☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.

☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.

☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins or at least 25 mm (1 in) using double spacing throughout.

☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

☐ Authors should keep copies of everything submitted.

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☐ The title page should contain the title of the article, which should be concise but informative;

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☐ First name, middle initial, and last name of each author, with highest academic degree(s);

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☐ Define all abbreviations except those approved by the International System of Units.

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Text

☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion.

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☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer reviewed Index Medicus journals. Abstracts appearing only in programs of meeting are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.

☐ Identify references in text, tables, and legends by arabic numbers (in parentheses, on line)

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus*.

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1. *Standard Journal Articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
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2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

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☐ Instead of original drawings, roentgenograms, or other material send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm.

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☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

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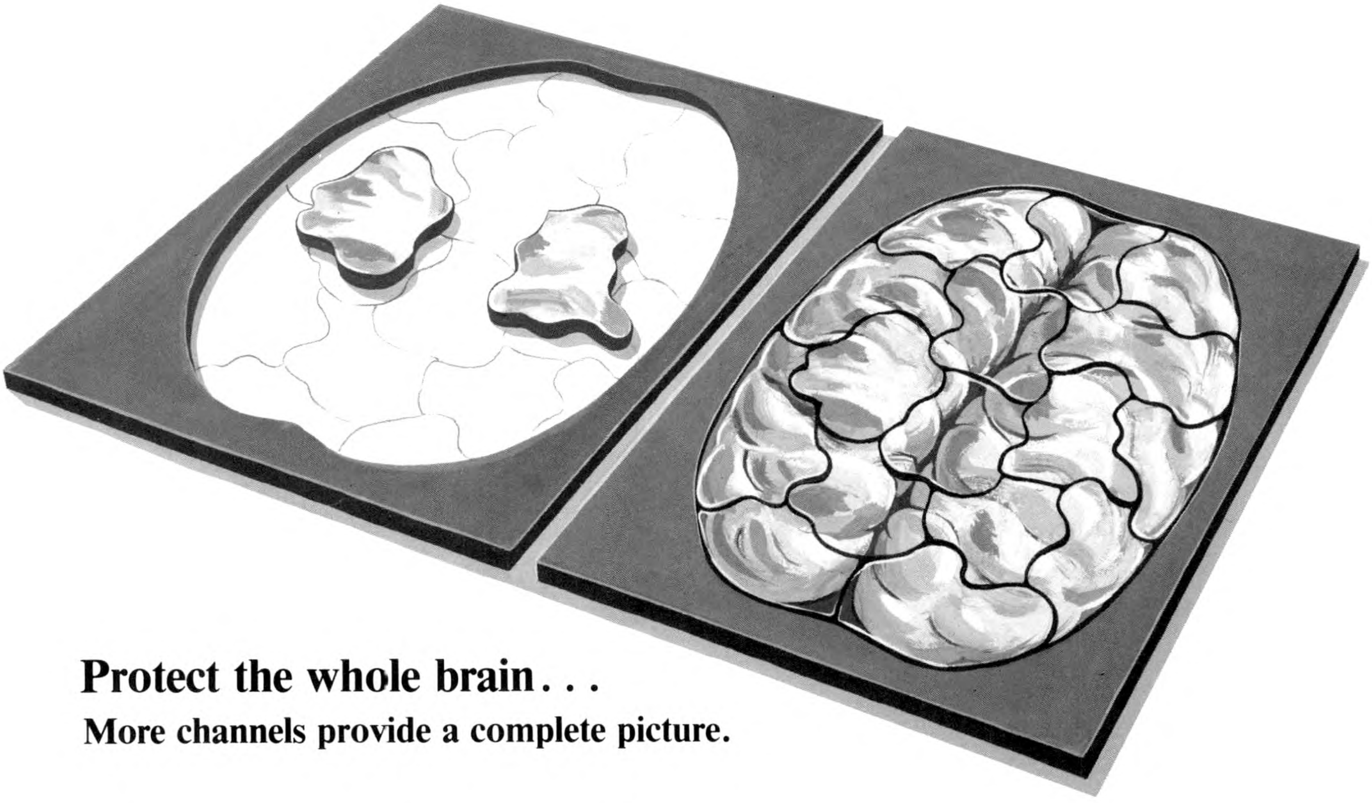

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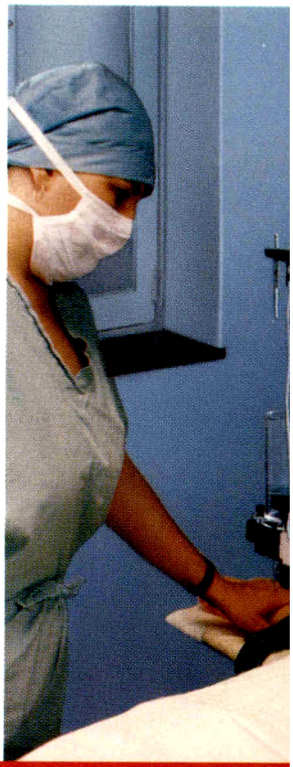

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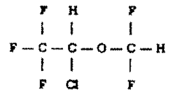
DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F{-}\overset{F}{\underset{F}{C}}{-}\overset{H}{\underset{Cl}{C}}{-}O{-}\overset{F}{\underset{F}{C}}{-}H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056, \; B = -1664.58, \; T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V F_V}{F_T (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336 Revised 10-85

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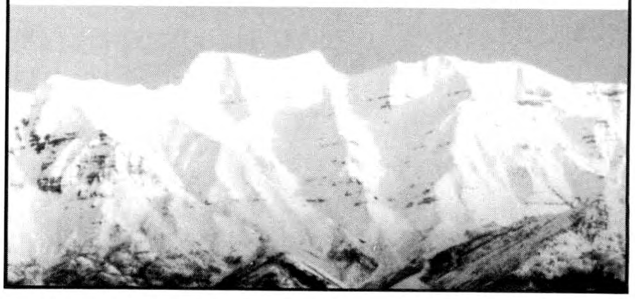

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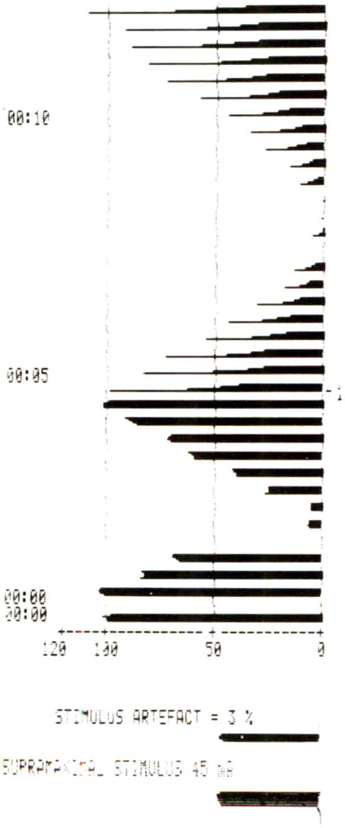

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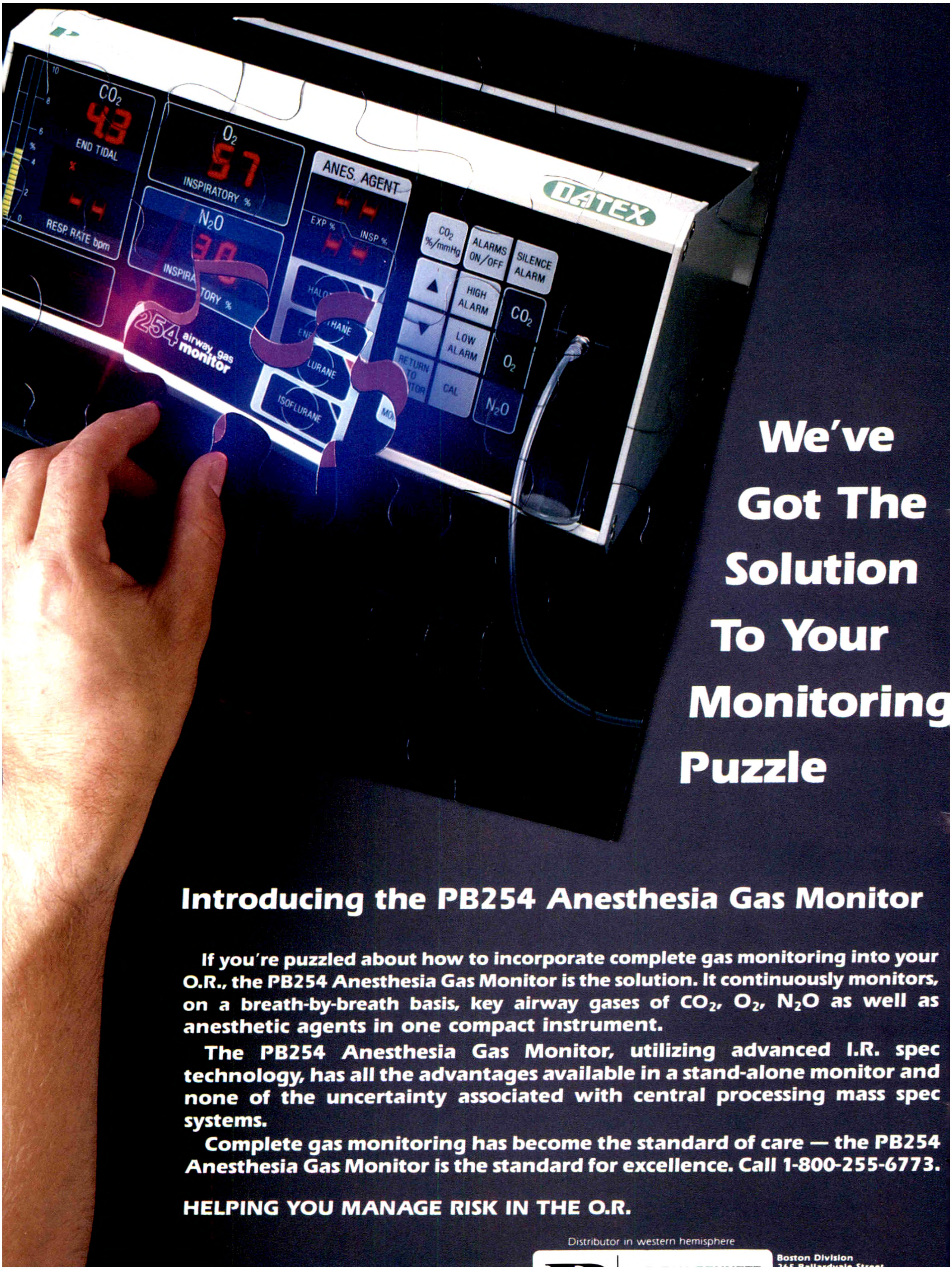

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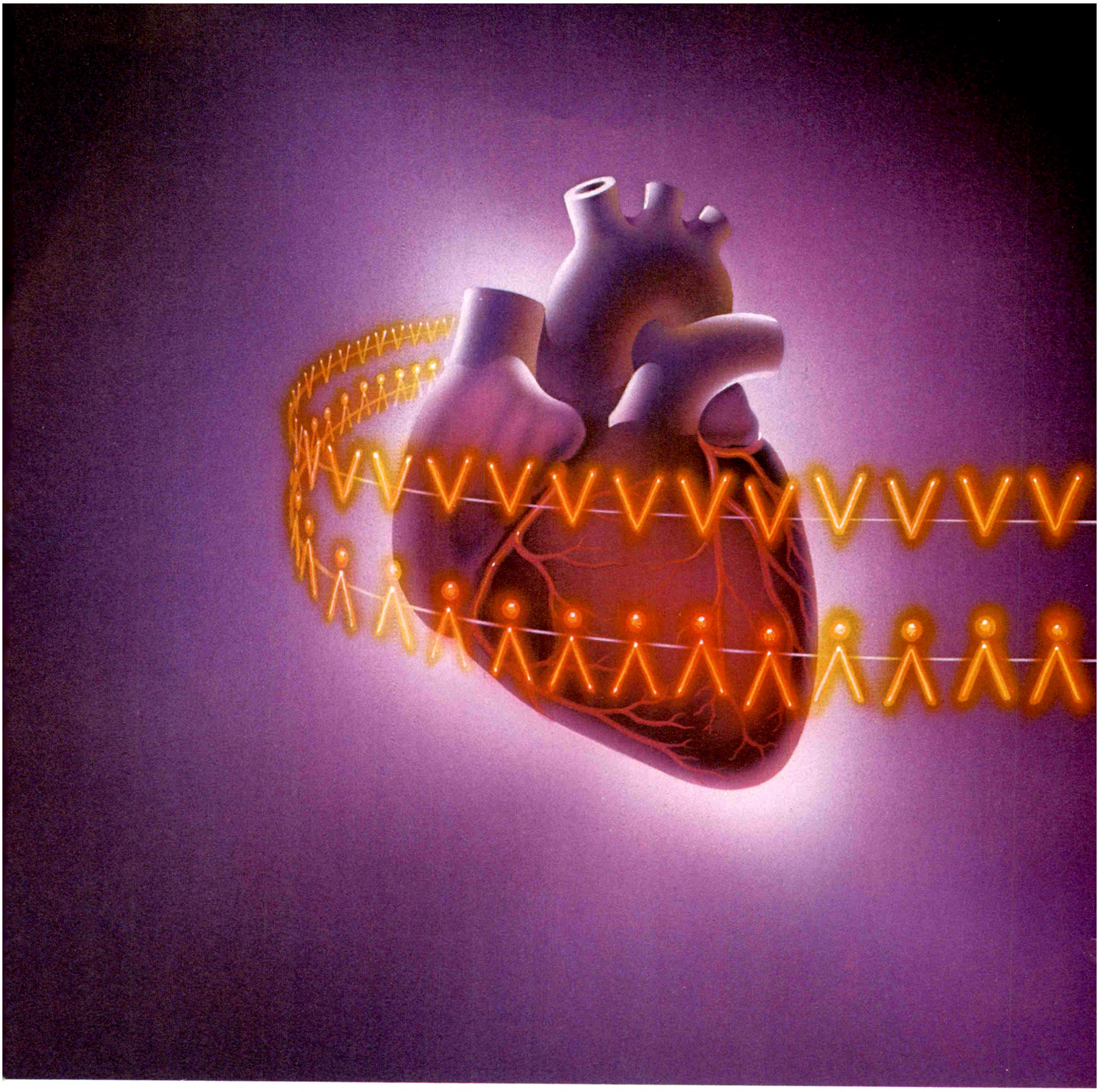

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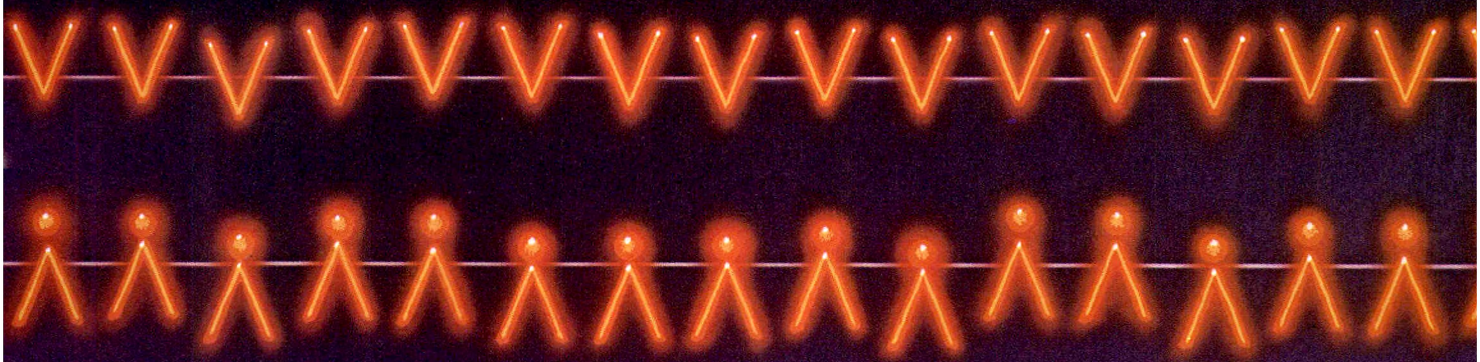

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Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involv-

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

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Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

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Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

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CAUTION

Federal (U.S.A.) law prohibits dispensing without prescription.

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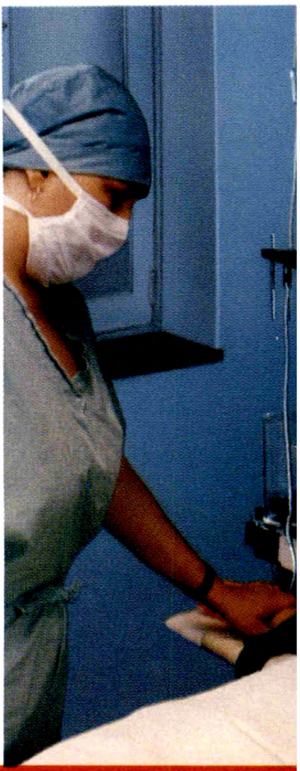

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Without *any* other agent or premedicant, isoflurane provides *every* action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and *ends* with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

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Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or $PaCO_2$ level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

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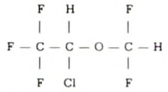
DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F-\overset{\displaystyle F}{\underset{\displaystyle F}{C}}-\overset{\displaystyle H}{\underset{\displaystyle Cl}{C}}-O-\overset{\displaystyle F}{\underset{\displaystyle F}{C}}-H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = °C + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V\, F_V}{F_T\, (P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336 Revised 10-85

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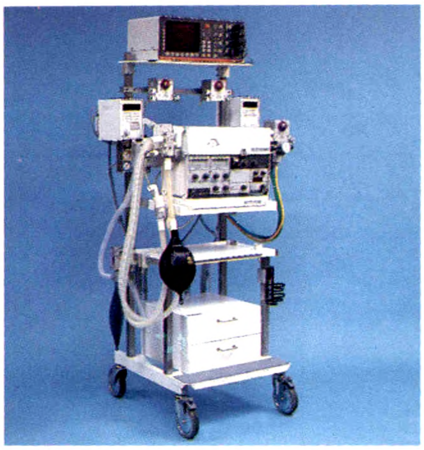

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Director EMG Laboratory, The Montreal General Hospital, Montreal, Quebec

Illustrated by **Margo Siminovitch, B.Sc., A.A.M.,** Director of Educational Resources, The Montreal General Hospital, Montreal, Quebec

Focal Peripheral Neuropathies is a comprehensive reference source for all physicians and surgeons who treat patients with acute and chronic peripheral nerve lesions. Neurologists and neurosurgeons, as well as hand and plastic surgeons, orthopedists, rheumatologists, and specialists in physical medicine and rehabilitation will find this well illustrated volume presents clinical and research information directly applicable to practice.

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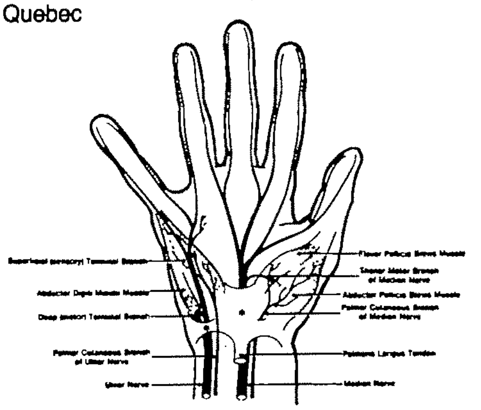
Superficial (sensory) Terminal Branch
Abductor Digiti Minimi Muscle
Deep (motor) Terminal Branch
Palmar Cutaneous Branch of Ulnar Nerve
Ulnar Nerve
Flexor Pollicis Brevis Muscle
Thenar Motor Branch of Median Nerve
Abductor Pollicis Brevis Muscle
Palmar Cutaneous Branch of Median Nerve
Palmaris Longus Tendon
Median Nerve

FIGURE 12.1 Palmar view of the right wrist and hand, showing the course and branching of the median and ulnar nerves. These nerves first divide into the common digital nerves, which then divide further to become individual proper palmar digital nerves. The transverse carpal ligament and its extension, which forms the roof of Guyon's canal, are marked with asterisks.

Contents

1 The Structure of the Peripheral Nervous System
2 Pathological Process Producing Focal Peripheral Neuropathies
3 Electrical Activity in Normal and Abnormal Nerves
4 The Evaluation of Patients with Focal Neuropathies
5 The Cervical Spinal Nerve Roots and Spinal Nerves
6 The Cervical Plexus and the Nerves of the Neck
7 The Brachial Plexus
8 The Nerves Arising from the Brachial Plexus
9 The Median Nerve
10 The Ulnar Nerve
11 The Radial Nerve
12 The Digital Nerves
13 The Cauda Equina, Lumbar and Sacral Nerve Roots, and Spinal Nerves
14 The Lumbosacral Plexus
15 The Sciatic Nerve, the Gluteal and Pudendal Nerves, and the Posterior Cutaneous Nerve of the Thigh
16 The Common Peroneal Nerve
17 The Tibial, Plantar, Interdigital, and Sural Nerves
18 The Femoral and Saphenous Nerves
19 The Lateral Cutaneous Nerve of the Thigh
20 The Obturator Nerve
21 The Iliohypogastric, Ilioinguinal, and Genitofemoral Nerves
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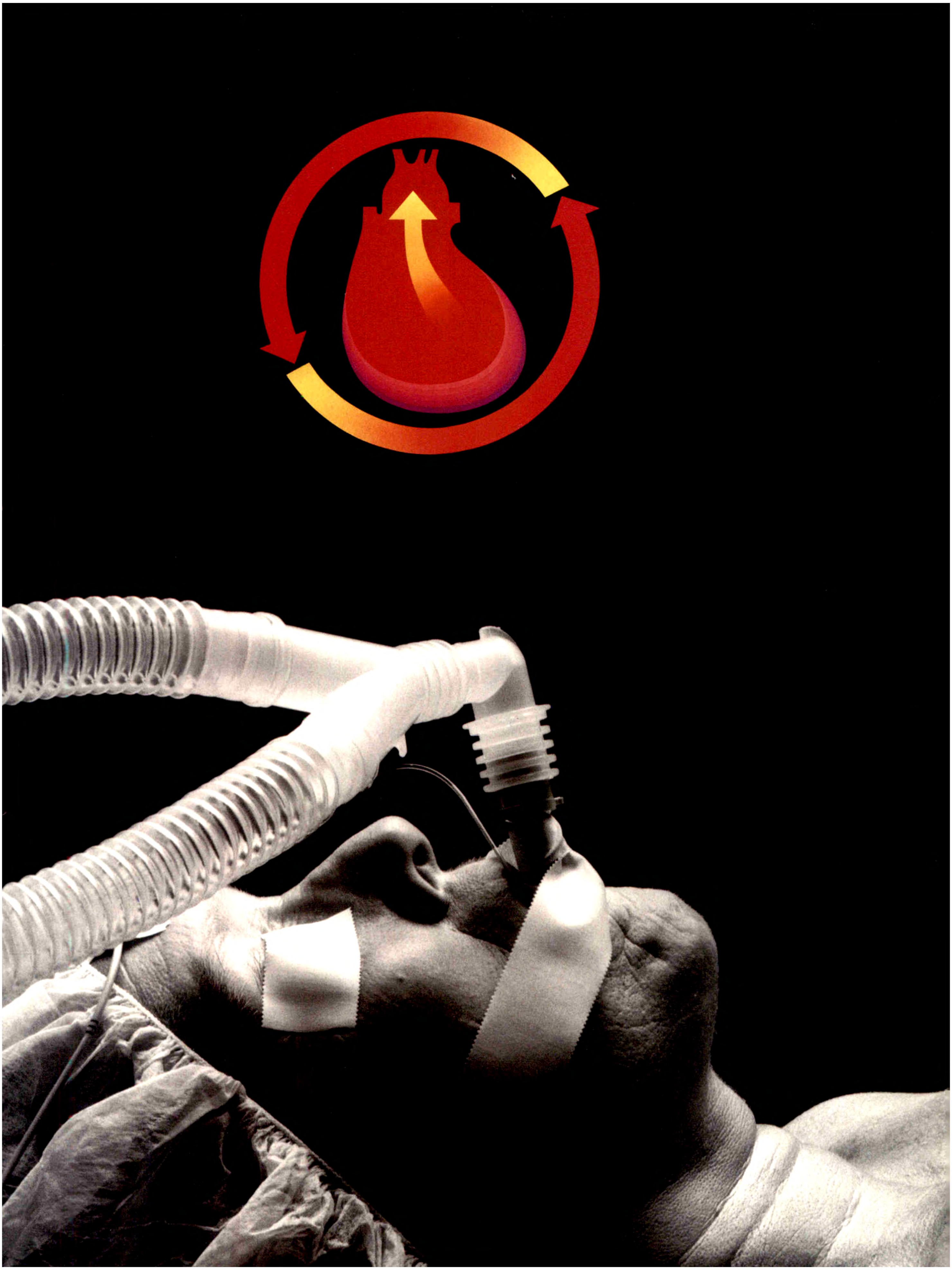


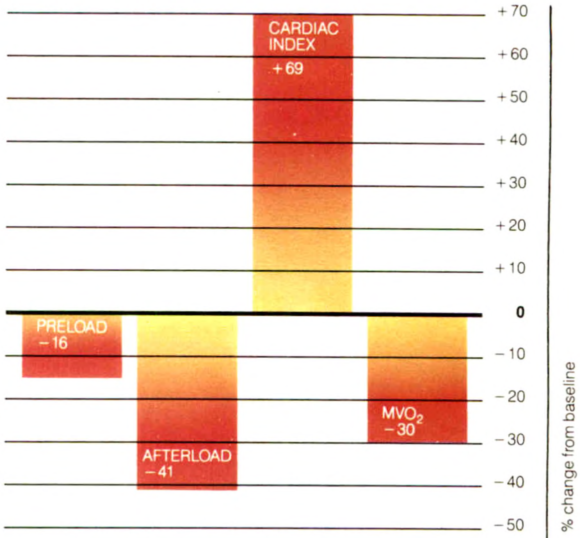
Dual action INOCOR® I.V. (AMRINONE) Inotropic plus vasodilating action in a single drug.

Two-in-one action can improve hemodynamic response after cardiac surgery.

In patients with congestive heart failure due to coronary artery disease, INOCOR I.V. increases CI and decreases preload and afterload without increasing MVO_2 or significantly increasing risk of arrhythmias.

*INOCOR I.V. is "...an extremely useful tool....I have been using amrinone...[for] inotropic support to wean patients from cardiopulmonary bypass and as a means of increasing [CI] in the post-bypass period."**

Roberta Hines, M.D.
Yale University School of Medicine
Yale University Hospital



†n = 8. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.[1]

Please see last page for important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations.

*Interview on file, Winthrop Pharmaceuticals.

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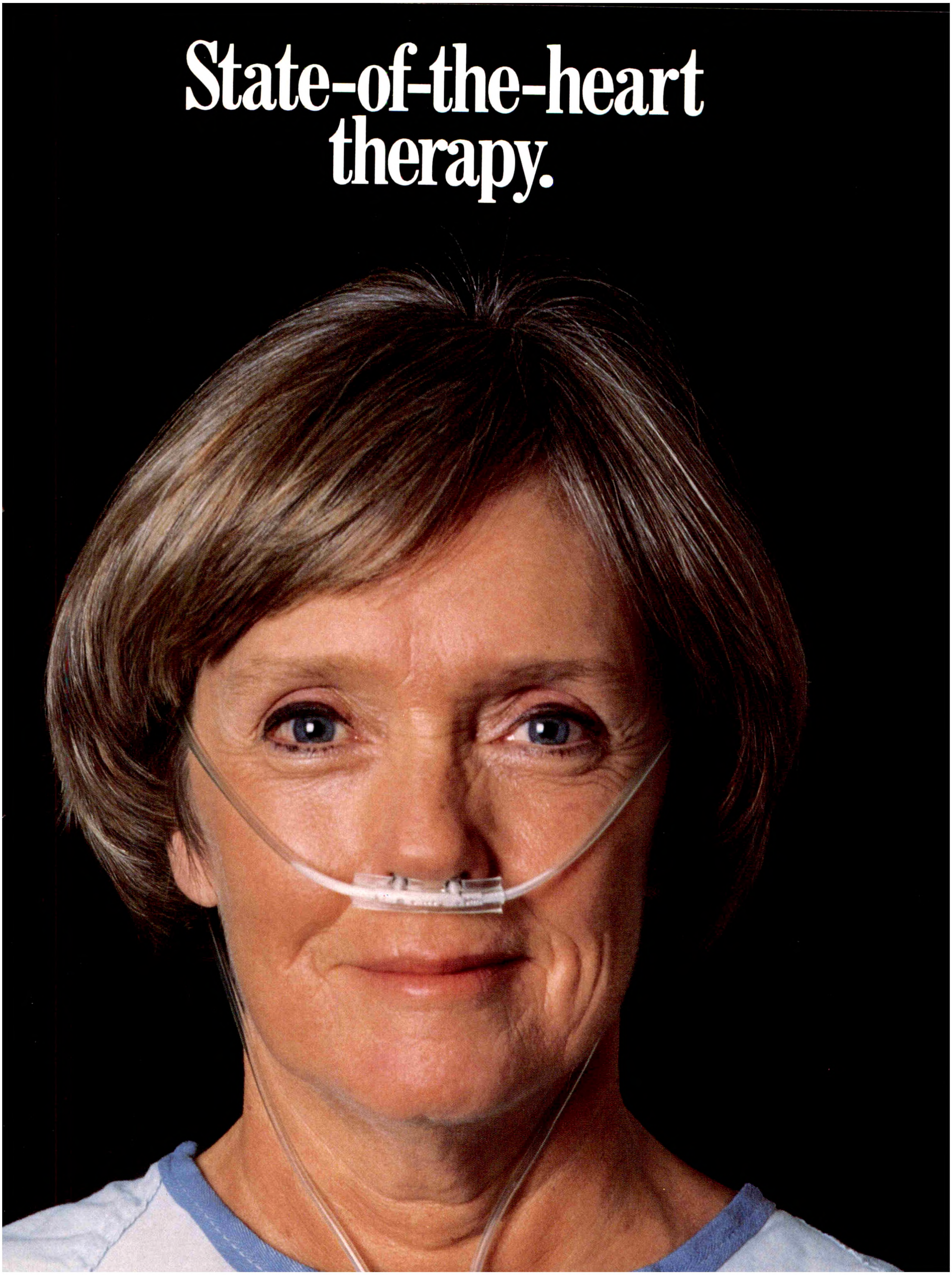
State-of-the-heart

Inocor® I.V.

(AMRINONE)


State-of-the-heart therapy.

INOCOR I.V.

Two-in-one dual inotropic and vasodilator action provides improved therapy for the cardiac surgery patient.

- Unlike catecholamines, INOCOR does not increase MVO_2 and can be used in ischemic patients with heart failure.
- Unlike catecholamines, INOCOR does not significantly increase risk of arrhythmias (see Precautions).
- Unlike catecholamines, INOCOR does not act on the beta receptors—may be effectively used in patients on beta blockers.
- INOCOR has not been shown to interact with anesthetic agents.

Please consult full product information before prescribing. A summary follows.

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General*: INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C*. In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is r certain, but possible hypersensitivity reactions should be considered in a patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrino clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotensi because of its vasodilator effect. If this occurs, amrinone administration shou be reduced or discontinued. No specific antidote is known, but gener measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductior* Asymptomatic platelet count reduction (to less than 150,000/mm³) may reversed within one week of a decrease in drug dosage. Further, with no chang in drug dosage, the count may stabilize at lower than predrug levels without a clinical sequelae. Predrug platelet counts and frequent platelet counts duri therapy are recommended to assist in decisions regarding dosa modifications.

Should a platelet count less than 150,000/mm³ occur, the followi actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have eith stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk excee the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were se infrequently with IV therapy, should severe or debilitating ones occur, t physician may wish to reduce dosage or discontinue the drug based on t usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepa toxicity has rarely been observed. If acute marked alterations in liver enzym occur together with clinical symptoms, suggesting an idiosyncratic hyperser tivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptor these nonspecific changes should be evaluated on an individual basis. T clinician may wish to continue amrinone and reduce the dosage or discontin the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containi INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCC lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water f injection.

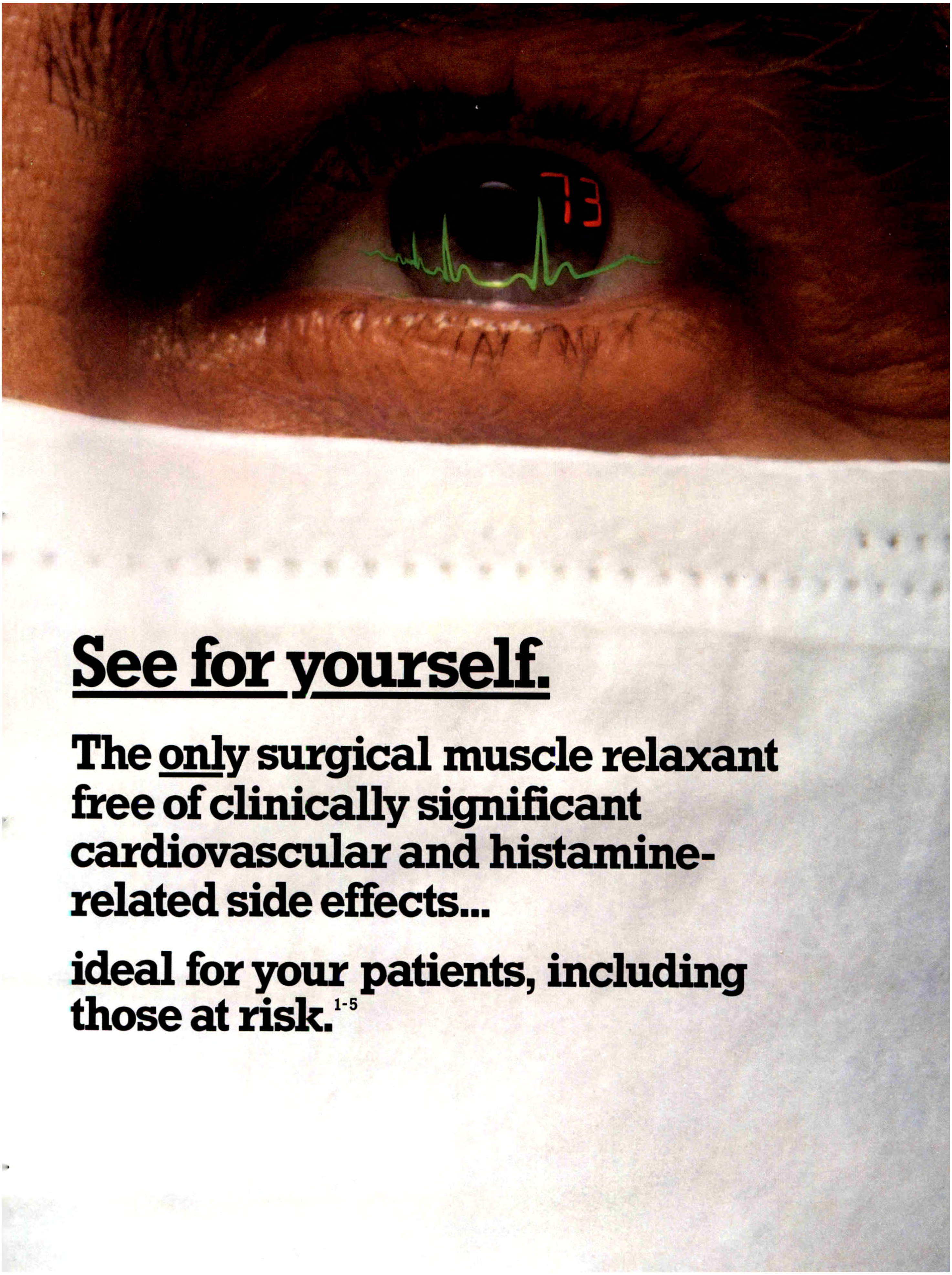
1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

State-of-the-heart

Inocor® I.V.

(AMRINONE)

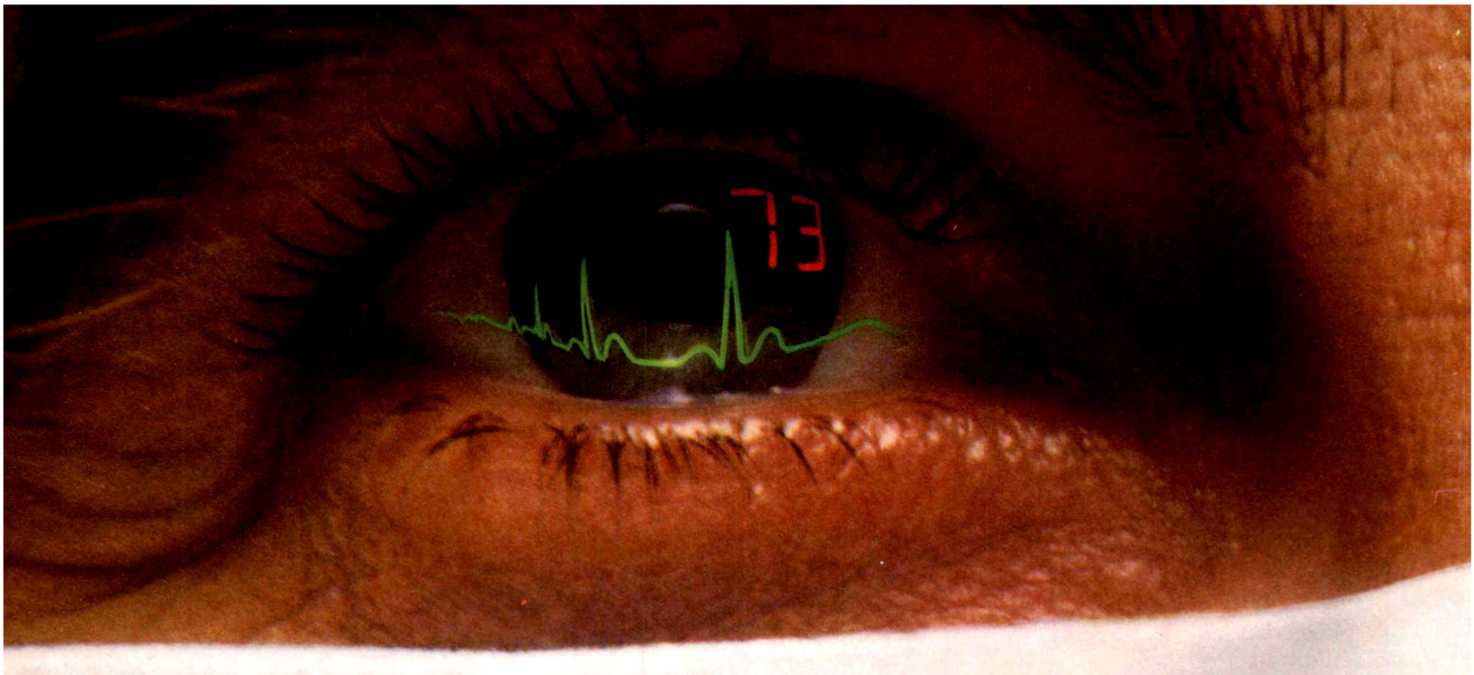
Winthrop
PHARMACEUTICALS



See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

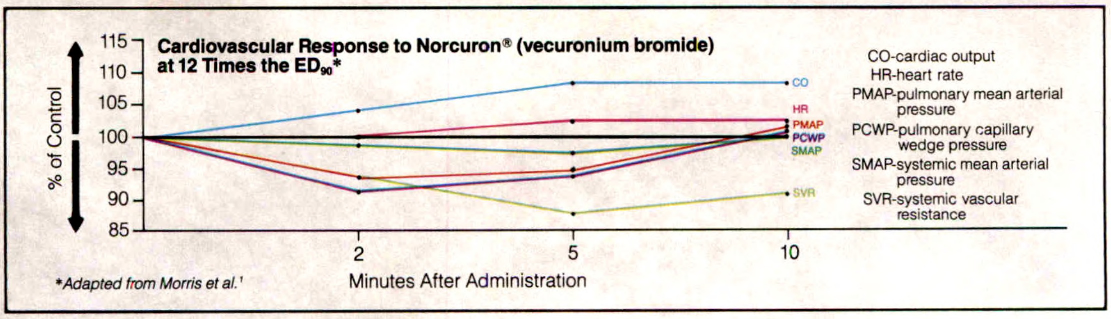
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



*Adapted from Morris et al.[1]

Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

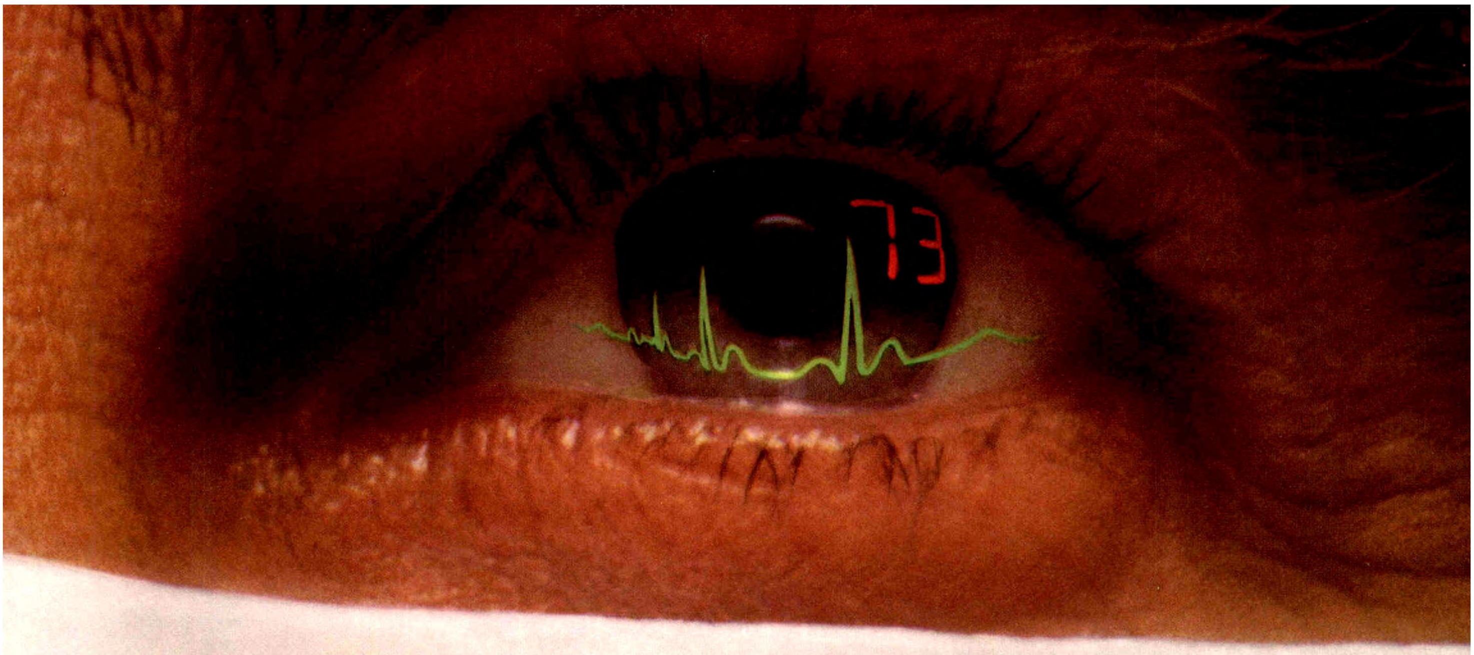
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
			Percent of Control		
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

*Adapted from Basta et al.[5]

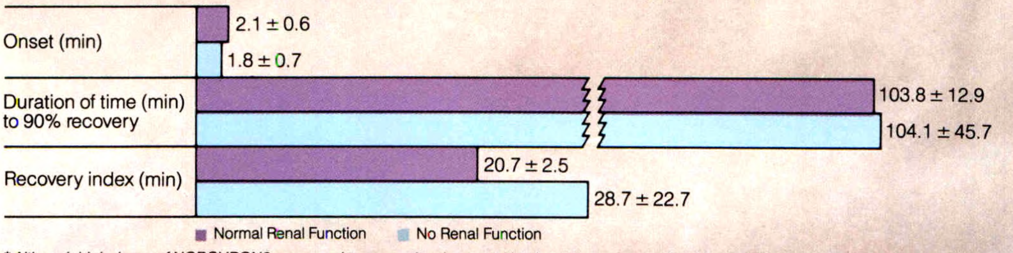
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



**Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.*
†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

NO REFRIGERATION REQUIRED

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

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DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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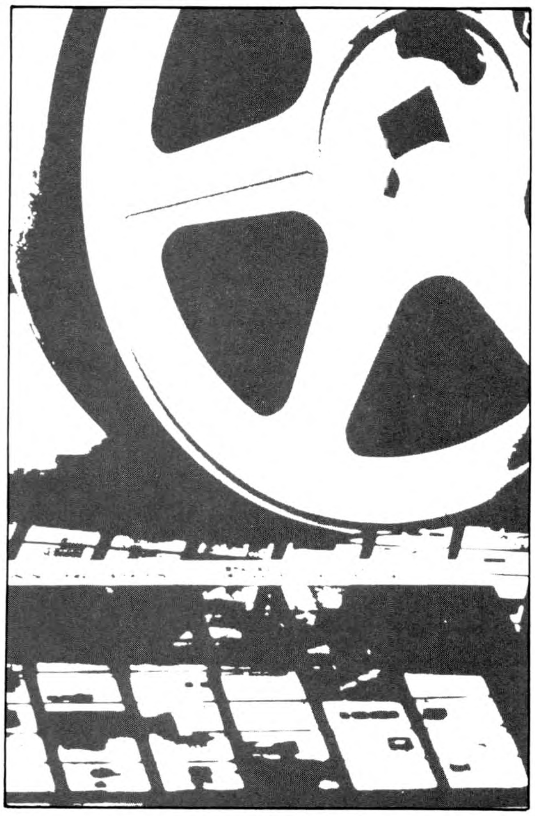

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Selective Increase in Cytoplasmic Calcium by Anesthetic in Lymphocytes from Malignant Hyperthermia-Susceptible Pigs

Amira Klip, PhD, Toolsie Ramlal, BS, Denise Walker, BS, Beverly A. Britt, MD, FRCCP, and M. Esther Elliott, MD

KLIP A, RAMLAL T, WALKER D, BRITT BA, ELLIOTT ME. Selective increase in cytoplasmic calcium by anesthetic in lymphocytes from malignant hyperthermia-susceptible pigs. Anesth Analg 1987;66:381–5.

Anesthetic-induced malignant hyperthermia in pigs and humans is characterized by muscle rigidity and rapid, often fatal, increases in body temperature. A defect in Ca^{2+} homeostasis has been suspected as underlying the disease, based on the preventive effect of dantrolene sodium, an agent thought to reduce Ca^{2+} levels in the cytoplasm. We describe here direct measurements of cytoplasmic ionized Ca^{2+} levels in lymphocytes from seven normal and 12 malignant hyperthermia-susceptible pigs, using the fluorescent indicator quin2. No differences in the concentration of cytoplasmic ionized Ca^{2+} were found in cells from malignant hyperthermia-susceptible pigs (160 ± 10 nM) relative to the controls (150 ± 10 nM). However, addition of halothane in vitro caused a significant increase (to 270 ± 30 nM) in lymphocytes from malignant hyperthermia-susceptible pigs, but not from normal pigs (180 ± 10 nM). The halothane-mediated increase in cytoplasmic ionized Ca^{2+} required extracellular Ca^{2+}. It is suggested that general anesthetics such as halothane increase the permeability of the cell surface to Ca^{2+}, and that this increase may, on its own or indirectly, increase the cytoplasmic level of ionized Ca^{2+} during a malignant hyperthermia crisis. The detection of a halothane-dependent increase in cytoplasmic ionized Ca^{2+} selectively in malignant hyperthermia-susceptible pigs could be the basis for a noninvasive test for malignant hyperthermia.

Key Words: HYPERTHERMIA—malignant. IONS—calcium.

Malignant hyperthermia (MH), caused in humans and several animal species by volatile anesthetics or depolarizing muscle relaxants, is marked by muscle rigidity, high fever, and a cascade of metabolic and electrolyte alterations that can lead to a fatal outcome (1–4). In susceptible humans and pigs, the MH crisis can be prevented by administration of the muscle relaxant dantrolene (5–7), which is believed to act by interfering with some step in the excitation–contraction pathway. It is thought that in isolated muscle fibers, dantrolene prevents the release of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm (although the exact mechanism whereby dantrolene exerts its therapeutic action in MH remains unknown) (8,9). Therefore, a role for Ca^{2+} has been suggested in the generation of the MH crisis (1–4,10). Using intracellular Ca^{2+} selective microelectrodes, Lopez et al. (11) recently reported that in the exposed peroneus longus muscle, the resting intracellular concentration of free Ca^{2+}, $[Ca^{2+}]_i$, was higher in an MH-susceptible pig than in a normal one. Halothane further increased $[Ca^{2+}]_i$ (12). Unfortunately, the microelectrode technique is restricted to large cells that can be impaled with both a voltage and a Ca^{2+} microelectrode. A muscle biopsy or an exposed intact muscle is required for this procedure. Moreover, in the above experiments (11,12), different fibers were generally impaled with the two types of electrodes (11), making it difficult to establish the exact value of $[Ca^{2+}]_i$.

Abbreviations Used in the Text

$[Ca^{2+}]_i$	Concentration of cytoplasmic ionized calcium
quin2/AM	Acetoxymethyl ester of quin2
MH	Malignant hyperthermia
HEPES	4-(-2-hydroxythyl)-1-piperazineethanesulfonic acid
EGTA	[ethylenebis(oxyethylenenitrilo)]tetraacetic acid

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Table 1. Response of Pig Muscle Fascicles to Halothane and Caffeine

Normal pigs				Malignant hyperthermia-susceptible pigs			
Pig no.	Hal. contracture[a] (g)	CSC[b] (mM)	CSCH[c] (mM)	Pig no.	Hal. contracture[a] (g)	CSC[b] (mM)	CSCH[c] (mM)
448	0	10	>2.0	451	0.25	3.3	0.29
453	0	>32	3.7	452	0.1	3.1	0.49
454	0	>32	3.7	457	0.45	1.4	0.14
475	0	13.3	3.7	458	0.2	4.2	0.64
490	0	16	2.0	459	0.4	2.8	0.21
491	0	25	>4.0	481	0.4	4.1	0.25
492	0	13.5	1.7	482	0.1	3.4	0.16
—	—	—	—	483	0.25	4.8	0.69
—	—	—	—	484	0.55	2.5	0.14
—	—	—	—	487	0.2	2.6	0.31
—	—	—	—	493	0.2	4.8	1.0
—	—	—	—	496	0.35	2.0	0.25

[a] Hal. contractures = contractures (g) observed in the presence of 1% halothane (1% in O_2:CO_2 95:5).

[b] CSC = caffeine specific concentration, i.e., concentration of caffeine (in mM) in the absence of halothane at which a contracture of 1.0 g is observed.

[c] CSCH = caffeine specific concentration in the presence of halothane, i.e., concentration of caffeine (in mM) in the presence of 1% halothane at which a contracture of 1.0 g is observed.

Lately it has become possible to determine $[Ca^{2+}]_i$ in cells of any size by the procedure described by Tsien et al. (13), which involves the use of fluorescent Ca^{2+} chelators such as quin2. This molecule is generated in the cytoplasm by hydrolysis of the precursor quin2 acetoxymethyl ester (quin2/AM) through action of cytosolic esterases. Quin2, being negatively charged, is unable to leave the cytoplasm, where its fluorescence increases as a function of the concentration of Ca^{2+}. By this procedure, $[Ca^{2+}]_i$ has been determined in a number of cells, including lymphocytes, platelets, and muscle cells in culture (14–17). Using isolated peripheral blood lymphocytes from normal and MH-susceptible pigs, we report here the effect of halothane on $[Ca^{2+}]_i$ measured by the fluorescence of quin2. We have presented a preliminary account of these results (J Gen Physiol 1986;88:33a).

Experimental Procedures

Normal and MH-susceptible Pietrain/Poland China pigs were obtained from Hanley's Farm, Ontario. Susceptibility to MH was determined by the halothane-caffeine contracture test (18). Normal pigs selected for this study were those whose muscle fascicles did not show contractures upon exposure to 1% halothane, and required >8.3 mM caffeine in the absence of halothane, and >1.2 mM caffeine in the presence of 1% halothane, to develop a 1.0 g contracture. The MH-susceptible pigs selected for this study were those whose muscle fascicles showed contractures with 1% halothane, and required <8.3 mM caffeine alone, or <1.2 mM caffeine in the presence of 1% halothane, to produce a 1.0 g contracture (18). The individual results are shown in Table 1.

$[Ca^{2+}]_i$ was determined fluorimetrically by the method of Tsien et al. (13) as described earlier (16,17). Peripheral blood lymphocytes were isolated as described by Elliott (19) and resuspended in 1 ml of bicarbonate-free RPMI-1640 culture medium containing 20 mM HEPES pH 7.4 (HEPES-RPMI). The cells were incubated with quin2/AM (1 μl of a 10-mM stock solution of quin2/AM in dimethyl sulfoxide was added per ml cell suspension, to give a final concentration of 10 μM) for 30 min at 37°C, washed twice by centrifugation in HEPES-RPMI, and resuspended in 0.2 ml of the same medium. (The stock solution of quin2/AM was kept at −20°C and wrapped in foil to protect it from light.)

Aliquots of 20 μl (approximately 5 × 10^5 cells) were used for the determination of $[Ca^{2+}]_i$ by addition into 1.5 ml of 120 mM NaCl, 0.5 mM EGTA, 3 mM KCl, 10 mM D-glucose, 20 mM HEPES-Na pH 7.3. Fluorescence was recorded in a 650-40 Perkin-Elmer spectrofluorometer (Norwalk, Conn.) at 339 nm of excitation (with a 3-nm slit width) and 485 nm emission (with a 15-nm slit width). These wavelengths were found to be the maxima for excitation and emission in the conditions of this study. Thorough mixing was achieved by magnetic stirring. The fluorescence readings (F) were calibrated after addition of 1.5 mM $CaCl_2$, by permeabilization to Ca^{2+} with 0.5 μM of the Ca^{2+} ionophore ionomycin ("I") (yielding the maximum fluorescence F_{max}). Under these conditions, Ca^{2+} flows into the cell down its concentration gradient. This addition was followed by displacement of Ca^{2+} with

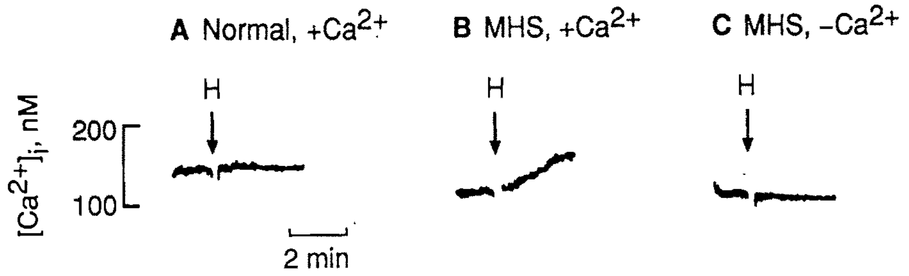

Figure 1. Fluorescence tracings of determinations of cytoplasmic ionized Ca^{2+} in lymphocytes from a normal pig (A) and a malignant hyperthermia-susceptible pig (B,C). $CaCl_2$ (1.5 mM) was added in A and B but not in C. Halothane (4 µl/ml) was added at "H" with a Hamilton microsyringe.

3 mM $MnCl_2$ ("Mn") (yielding F_{Mn}). Free cytoplasmic calcium was calculated from the equation: $[Ca^{2+}]_i = 115(F - F_{min})/(F_{max} - F)$, where $F_{min} = 1/6(F_{max} - F_{Mn}) + F_{Mn}$ (14,15). It must be stated that measurements of $[Ca^{2+}]_i$ with quin2 are calculated based on the dissociation constant (K_D) of the quin2/Ca^{2+} complex (115 nM). This value was calculated by Tsien et al. (13) and corroborated by us, using synthetic solutions that mimic—but do not exactly reproduce—the cytoplasmic milieu. Thus, in view of the possible effects of the particular ionic composition of the cytoplasm, and of the presence of organic substances that may alter the cytoplasmic dielectric constant, the value of K_D used in this (and all other studies with quin2) is only an approximation. Therefore, values of $[Ca^{2+}]_i$ have been rounded off to the nearest second digit. In spite of the above caveat, the fluorescence of quin2 in the cytoplasm is proportional to $[Ca^{2+}]_i$. Moreover, changes in $[Ca^{2+}]_i$ are reliably detected by dyes such as quin2 (13–15).

Results

Figure 1*A* shows a typical fluorescence tracing of $[Ca^{2+}]_i$ in lymphocytes from a normal pig. In the experiment illustrated, $[Ca^{2+}]_i$ was 125 nM in the presence of 1 mM (final concentration) extracellular Ca^{2+}. Addition of halothane (4 µl/ml) did not change the level of $[Ca^{2+}]_i$ appreciably. Figure 1*B* shows a typical fluorescence tracing of $[Ca^{2+}]_i$ in lymphocytes from an MH-susceptible pig. In the presence of 1 mM extracellular Ca^{2+}, the level of $[Ca^{2+}]_i$ was 110 nM. In contrast to the observation with cells from the normal pig, addition of halothane (4 µl/ml) increased $[Ca^{2+}]_i$ in lymphocytes from the MH-susceptible pig to a value of 165 nM. The increase was not observed in the absence of extracellular Ca^{2+} (Fig. 1*C*). These data suggest that halothane increases $[Ca^{2+}]_i$ by increasing the permeability of the plasma membrane to the cation.

Table 2 shows the individual results, as well as the averages, of measurements of $[Ca^{2+}]_i$ in lymphocytes from seven normal and 12 MH-susceptible pigs. The results indicate that with 4 µl/ml halothane, $[Ca^{2+}]_i$ increased significantly only in the MH-susceptible group. The dose of halothane used in this study (4 µl/ml or 38 mM) did not affect cell viability in either quin2 loaded or unloaded cells, determined by exclusion of trypan blue and by retention of lactic dehydrogenase. This concentration of halothane is severalfold higher than the pharmacological doses of anesthetic. A halothane concentration of 3.34 mM has been detected in the brain of halothane-anesthetized rats (20). We have recently observed that with lower concentrations of halothane (1 mM final, added in dimethyl sulfoxide), $[Ca^{2+}]_i$ was again increased in lymphocytes from MH-susceptible pigs but not from normal pigs (not shown). Dimethyl sulfoxide itself was without effect in either group.

Discussion

The advantages of determining $[Ca^{2+}]_i$ with fluorescent dyes such as quin2 over Ca^{2+}-microelectrodes have been stated repeatedly in the past two years, and consist primarily of being able to report $[Ca^{2+}]_i$ in cells of any size, to be confined to the cytoplasm, and, under conditions such as those used in this study, to cause minimal damage to the cells (13,17,21–23). Indeed, in control experiments we found that the viability of quin2 loaded cells was not different from that of unloaded cells, in either the presence or absence of halothane.

The results of this study indicate that:

1. The basal level of $[Ca^{2+}]_i$ was equal in peripheral blood lymphocytes from normal and MH-susceptible pigs.
2. Halothane selectively enhanced $[Ca^{2+}]_i$ in cells from MH-susceptible pigs but not from normal pigs. The increase measured may be an underestimate of the absolute increase that takes place, if a limited amount of Ca^{2+} enters the cell under halothane, since quin2 can buffer intracellular Ca^{2+} (24,25). We have also observed large increases in $[Ca^{2+}]_i$ in indo-1 loaded lymphocytes from MH-susceptible (but not control) pigs (Klip et al., unpublished). Indo-1 is a

Table 2. Effect of Halothane on Lymphocyte Cytoplasmic Free Calcium Concentration

Normal pigs				Malignant hyperthermia-susceptible pigs			
	Cytoplasmic free calcium (nM)				Cytoplasmic free calcium (nM)		
Pig no.	−Halothane	+Halothane	Δ	Pig no.	−Halothane	+Halothane	Δ
448	130 (2)	160 (2)	30 (2)	451	120 ± 20 (4)	210	80
453	130 (2)	150 (2)	20 (2)	452	180 (2)	250 (2)	70 (2)
454	100 (2)	140 (2)	40 (2)	457	160 (2)	310	150
475	190	230	40	458	180 ± 40 (3)	280 (2)	90 (2)
490	160 ± 20 (6)	160 ± 40 (4)	0 (4)	459	180 (2)	280 (2)	100 (2)
491	210 ± 40 (5)	240 ± 40 (5)	30 (5)	481	160 ± 8 (3)	230 (2)	70 (2)
492	160 ± 15 (6)	200 ± 30 (4)	40 (4)	482	190 ± 60 (6)	280 ± 90 (5)	90 (5)
—	—	—	—	483	220 ± 50 (3)	360 (2)	120 (2)
—	—	—	—	484	190 ± 20 (6)	320 ± 50 (3)	140 (3)
—	—	—	—	487	100 ± 10 (5)	140 (2)	50 (2)
—	—	—	—	493	160 ± 20 (12)	490 ± 120 (5)	370 (5)
—	—	—	—	496	80 ± 10 (4)	130 (2)	60 (2)
Average:	−Halothane	+Halothane		Average:	−Halothane	+Halothane	
	150 ± 10 (7)	180 ± 10 (7)[a]			160 ± 10 (12)[b]	270 ± 30 (12)[c]	

Cytoplasmic ionized Ca^{2+} was determined in quin2-loaded lymphocytes suspended in isotonic saline solution containing 1 mM CaCl_2. When present, 4 μl/ml halothane was added and calcium levels were determined immediately after. Results are the mean ± SEM of (*n*) determinations in single blood samples, except for the averages, in which n = number of pigs. Δ represents the mean difference in cytoplasmic free Ca^{2+} without and with halothane in each sample (using only those determinations in which halothane was tested; hence Δ is not the algebraic difference of *all* data without and with halothane).

Student t = test, two tail: [a]$P > 0.05$ for N, + vs − halothane. [b]$P > 0.05$ for MH vs N, − halothane. [c]P (not paired) < 0.02 for MH vs N, + halothane; P (paired) < 0.001 for + vs − halothane.

fluorescent Ca^{2+} indicator that is used at lower intracellular concentrations and, therefore, has a lower chelating effect on cytoplasmic Ca^{2+} (24).

3. Extracellular Ca^{2+} was the source for the increase in $[\mathrm{Ca}^{2+}]_i$, but we cannot differentiate at present as to whether the entry of extracellular Ca^{2+} per se explains the total increase in $[\mathrm{Ca}^{2+}]_i$ or whether it would only be the trigger for further release of Ca^{2+} from intracellular stores.

In muscle, both the muscle plasma membrane (26–28) and the sarcoplasmic reticulum (29) have been suggested as possible sites of action of halothane in the triggering of the MH crisis. Whereas one cannot infer that the lymphocyte is a model of the muscle, it is possible that similar mechanisms operate in these and other cells that result in the regulation of $[\mathrm{Ca}^{2+}]_i$. In this regard, it is interesting to note that macrophages possess a caffeine-sensitive, Ca^{2+}-induced Ca^{2+} release mechanism very similar to that of the sarcoplasmic reticulum of skeletal muscle (30).

As stated above, Lopez et al. have reported that the resting $[\mathrm{Ca}^{2+}]_i$ is higher in skeletal muscle fibers of MH-susceptible pigs than of normal pigs (11), but still below the threshold level that induces contraction. This observation is in contrast with the results reported here with pig lymphocytes (in which the resting levels of normal and MH-susceptible pigs were indistinguishable), and the basis for the difference remains to be established when the two techniques used to determine $[\mathrm{Ca}^{2+}]_i$ are compared directly. However, in skeletal muscle fibers of MH-susceptible pigs, halothane further increased $[\mathrm{Ca}^{2+}]_i$ (12), in agreement with the reports in the present study. Given that a sustained increase in $[\mathrm{Ca}^{2+}]_i$ can induce muscle contracture and rigor, it is tempting to speculate that, in analogy to what occurs in lymphocytes, the primary action of halothane in muscle of MH-susceptible individuals could be to increase the permeability of the cell surface to Ca^{2+}. The increase in $[\mathrm{Ca}^{2+}]_i$ could directly, or through Ca^{2+}-induced Ca^{2+} release, cause a further increase in $[\mathrm{Ca}^{2+}]_i$, leading to increased rigidity and consequent heat production. Moreover, it is possible to suggest that peripheral blood lymphocytes could be used in the future to establish a relatively noninvasive assay to determine susceptibility to MH, based on the increase in $[\mathrm{Ca}^{2+}]_i$ caused by halothane in vitro.

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Intraoperative Transesophageal Color Flow Mapping:

Initial Experience

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Intraoperative transesophageal color flow mapping: initial experience. Anesth Analg 1987;66:386–90.

Transesophageal Doppler color flow mapping (TEDCFM) is a new ultrasound modality now being developed. It provides a convenient, noninvasive way to image cardiac anatomy and intracardiac blood flow that is applicable to intraoperative use. We describe its use in one normal subject and seven cardiac surgical patients. Blood flow characteristics as visualized by TEDCFM are described for these patients. Transesophageal Doppler color flow mapping provided specific information about the presence, site, and severity of mitral regurgitation, aortic regurgitation, and interatrial shunting. Paravalvular leak was detected in one patient after mitral valve replacement. The intimal tear of a type I aortic dissection was located with positive identification of the true and false lumina. A high incidence of mild asymptomatic mitral regurgitation was found in patients undergoing coronary artery bypass grafting (CABG).

Key Words: HEART—function. MEASUREMENT TECHNIQUE—transesophageal color flow mapping.

Transesophageal two-dimensional echocardiography and Doppler echocardiography are ultrasound techniques presently used by anesthesiologists. Transesophageal Doppler color flow mapping puts these two technologies together to provide new diagnostic information that will improve our understanding of intracardiac blood flow in physiologic and pathophysiologic states. There is rich clinical potential for such information in anesthesiology, where hemodynamic management can be crucial to optimize forward blood flow, and where patients with various cardiac disorders are anesthetized for corrective surgery. Flow characteristics associated with valve stenosis and incompetence and complex cardiac defects and their surgical corrections can now be evaluated intraoperatively. Such timely information may enable the surgeon to better judge the efficacy of the operation performed and may assist the anesthesiologist in his physiologic and pharmacologic interventions, thus resulting in better and more economical patient care.

Theoretical Basis for Color Flow Mapping

Moving red blood cells have the ability to "backscatter" ultrasound waves. Blood flow, therefore, can be observed by the reflection of ultrasound from the cells in blood. Velocity and direction of flow relative to a stationary transducer derives from the principle that an ultrasound wave of known frequency striking a moving red blood cell is reflected back at an altered frequency depending on the velocity of the red cell (Doppler principle) (1).

Before the development of color flow mapping, Doppler blood flow information could be derived from only one area at a time; the echocardiographer directed a pulse of ultrasound to a specific point in the heart (sample volume) that could then be characterized for velocity and direction of flow. Mapping of all the blood flow in the heart required that multiple sampling points be interrogated sequentially. Also, Doppler information was presented as an audible signal, or as a printed time-interval histogram.

With Doppler color flow mapping, pulses of ultrasound are directed into and received back from multiple sampling points along several lines of sight within the sector arc of a two-dimensional echocardiographic image (see Fig. 1). The entire image can be scanned in 66 msec or less, with the blood flow at each point being indicated by a color. As shown by the color notation at the top right corner of Figure 1, blood flowing away from the transducer is shown in blue,

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and flow towards the transducer appears red. It follows that if the ultrasound beam emitted by a transducer strikes blood flowing at right angles to it, the Doppler shift will be negligible and the net blood flow cannot be measured. The magnitude of flow velocity is indicated by the brightness of color; turbulence, representing varying velocities of blood within a sample volume, appears as a mosaic pattern of color. Thus, the blood flow is characterized according to its direction, magnitude, velocity, and turbulence by a color map, presented in real time directly on the two-dimensional cardiac image (2).

The same ultrasound transducer is used simultaneously for imaging and Doppler. Reflected ultrasound waves are separated electronically into two parts; high amplitude components reflected from cardiac structures provide the two-dimensional cardiac image and low amplitude waves from moving red blood cells provide blood flow information. Cardiac structures are displayed in a monochrome mode whereas blood flow velocity is presented in color.

Color Reversal or Aliasing

The maximum blood flow velocity that can be measured by pulsed Doppler techniques is limited by the pulse repetition frequency (PRF) of the system. Velocities exceeding the Nyquist limit (½ PRF) are distorted and appear as color reversal. Thus blue areas may develop a central zone of red and red areas may develop a central zone of blue. This frequency aliasing represents a potential source of error in interpretation of Doppler flow information (2), but also serves to highlight very high velocity jets of blood flow associated with pathologic lesions.

Methods

A prototype Hewlett-Packard TEDCFM transducer was used. Measuring 9 × 5 mm, this phased array transducer is no larger than similar conventional transesophageal transducers but contains 64 elements, operating at 5 MHz, which provides a higher resolution image than previously available. Flexibility of the endoscope and the technique for insertion into the esophagus is unchanged. The transducer cable is connected to a standard Hewlett-Packard echocardiograph (77020 AC) incorporating a color imaging module. Standard black and white images are displayed on the video screen with a 90° sector arc. The sector arc may be narrowed to provide a higher real-time frame rate.

This TEDCFM transducer was used in nine subjects including one awake normal volunteer and eight anesthetized patients undergoing cardiac surgery for various disorders: excision of left atrial myxoma (one patient); excision of right atrial thrombus (one patient); aortic valve replacement (one patient); mitral valve replacement (one patient); Bentall procedure (one patient); coronary artery bypass grafting (three patients).

In the awake subject, held fasting for 8 hr prior to the study, 0.5% tetracaine was sprayed into the oropharynx to facilitate passage of the endoscope. No sedation was necessary. In the anesthetized patients the endoscope was inserted after tracheal intubation, using a small amount of lubricating gel. The endoscope was advanced into the esophagus to record short and long axis images as appropriate to define the anatomy and blood flow characteristics.

Results

Technical Aspects

The endoscope was inserted without difficulty in all subjects. Image quality was excellent in each subject. On the black and white display, resolution was sufficient in all patients to define the small blood vessels, e.g., the left main coronary artery and its bifurcations into the circumflex and left anterior descending coronaries, the great cardiac vein, and the pulmonary veins. Definition of papillary muscles, chordae tendineae, endocardium and epicardium was markedly superior to other transesophageal images that we have seen.

Color Imaging

Color imaging in the short axis, where the general direction of blood flow is at right angles to the ultrasound beam, revealed little color data. In the long axis image, however, where blood flow is predominantly in a direction parallel to the ultrasound beam, there was significantly more color data.

1. Normal flow (1 subject). In the long axis view, with the transducer positioned posterior to the left atrium and directed caudad towards the cardiac apex, blood flow appeared as follows: During rapid filling of the left ventricle in early diastole, the left atrium and ventricle were filled with blue except for the left ventricular outflow tract appearing red and a central zone of red between the mitral valve leaflets. During systole, the left ventricle appeared red with some mixing of red and blue in the outflow tract. The left atrium remained blue or became colorless.

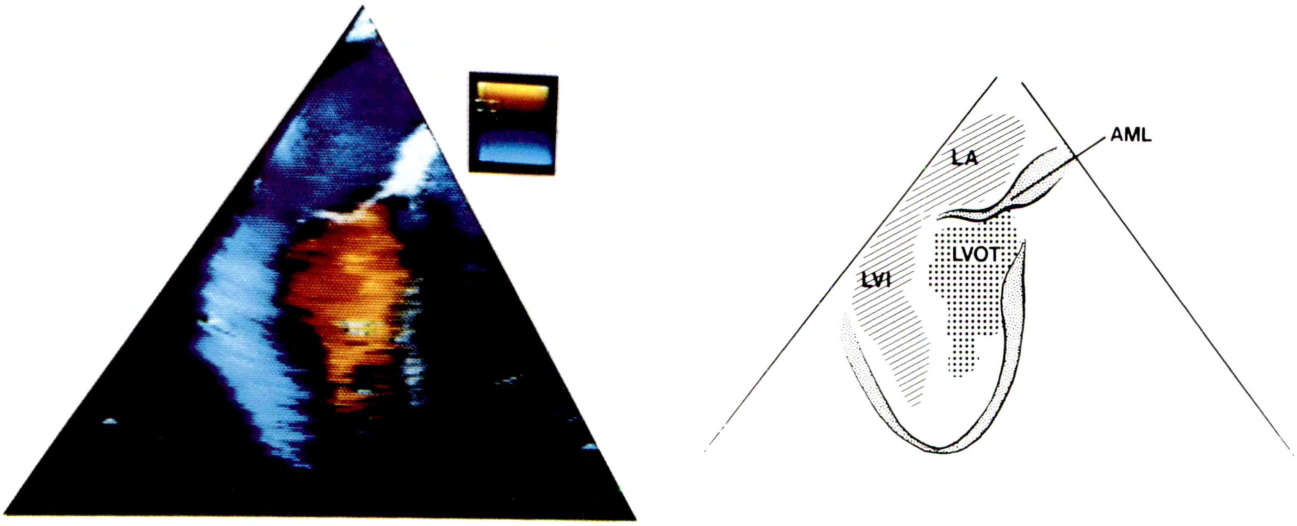

Figure 1. Doppler color flow mapping (left) and schematic diagram (right) of long axis view illustrating normal blood flow during diastole. Abbreviations: LA, left atrium; LVI, left ventricular inflow; LVOT, left ventricular outflow tract; AML, anterior mitral leaflet.

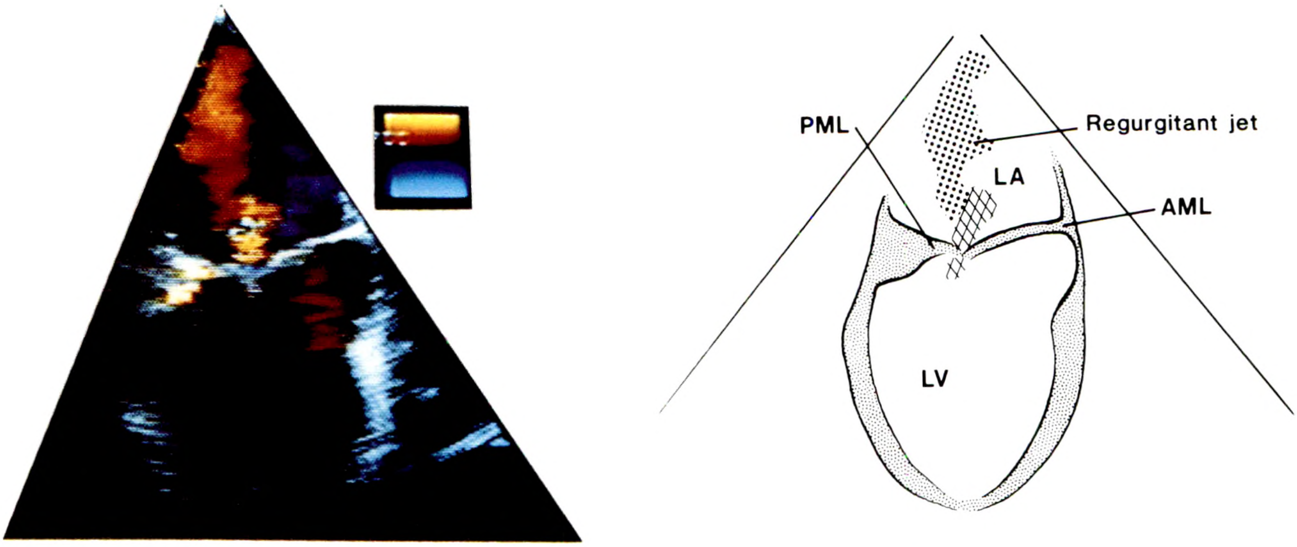

Figure 2. Doppler color flow mapping (left) and schematic diagram (right) of mitral regurgitation. Long axis view during systole. Turbulent flow at the mitral valve orifice appears as a mosaic of color, indicated by cross-hatching on the line drawing. Abbreviations: LA, left atrium; LV, left ventricle; PML, posterior mitral leaflet; AML, anterior mitral leaflet.

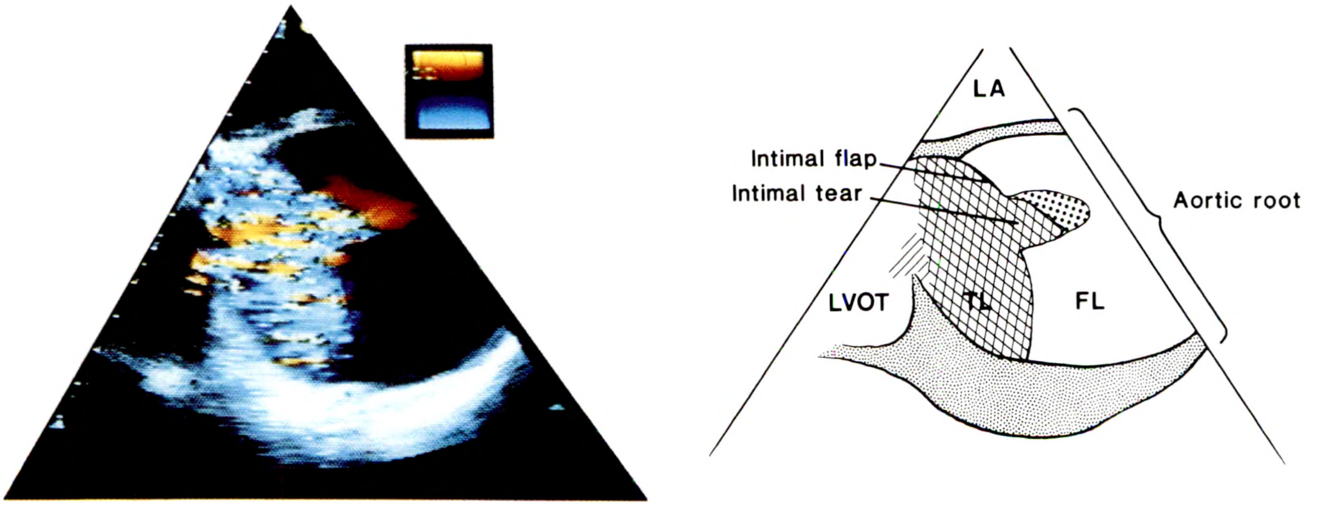

Figure 3. Doppler color flow mapping (left) and schematic diagram (right) of aortic dissection, Type I. Short axis view across dilated aortic root. Turbulent flow occupies the true lumen (TL) escaping into the false lumen (FL) via the intimal tear. LA, left atrium; LVOT, left ventricular outflow tract.

2. Aortic stenosis (1 subject). During systole both long and short axis views across the aortic valve revealed a mosaic pattern of color indicating turbulent flow at the valve and in the aortic root. This was replaced in diastole by faint red and blue, probably representing lower velocity eddy currents.
3. Aortic regurgitation (2 subjects). In a long axis view, the left ventricular outflow tract and aortic root appeared red in systole. During diastole a mosaic of color extended from the aorta back into the left ventricle as far as the apex, representing turbulent regurgitant flow.
4. Mitral stenosis (1 subject). In the long axis view, diastolic flow through the valve appeared as a mosaic of color representing turbulent flow through the stenotic valve. The left ventricular cavity appeared blue.
5. Mitral regurgitation (6 subjects) (Fig. 2). In the long axis view, a flame of red and yellow color appeared in the left atrium at the onset of systole. The flame appeared to arise at the valve annulus and occasionally had a mosaic center. In one case a small red flame appeared after mitral valve replacement at the lateral edge of the prosthetic valve.
6. Aortic dissection, type I (1 subject) (Fig. 3). Short axis views across the dilated root of the aorta revealed a brilliant mosaic of color filling the true lumen during systole. Faint patches of blue and red were seen occasionally in the false lumen. The passage of color from the true lumen to the false lumen through a small defect in the intimal flap seen on the monochrome image confirmed the entrance site of the intimal tear.
7. Atrial tumors (2 patients). Definition of both a right atrial thrombus and a left atrial myxoma was excellent on monochrome images. Blood flow around these atrial tumors was indicated by dull blue and red colors during diastole. After resection of the left atrial myxoma and placement of a pericardial patch graft to the interatrial septum a small red "flame" appeared in the left atrium originating from the septum cephalad to the coronary sinus. This suggested a small right-to-left shunt at the suture line.

Discussion

Clinical use of TEDCFM has not previously been reported. A prototype system designed for simultaneous blood flow and two-dimensional cardiac imaging was developed with a transthoracic transducer in 1982 (3–5). More recently, Miyatake et al. (6) have described the use of transthoracic DCFM in 20 healthy subjects and 100 cardiac patients. They provided a detailed description of mitral inflow and aortic ejection as well as regurgitant flow. Intraoperative color flow mapping has also been reported, by Takamoto et al. (7), using a sterile on-the-heart transducer. In their study of 33 patients with valvular disease, congenital heart disease, and vascular disease, DCFM was useful in evaluating the competence of prosthetic valves, the magnitude of interatrial shunt flow after balloon atrial septostomy, and in defining the extent of dissecting aortic aneurysms. Switzer and Nanda (8) have found that various maneuvers or drugs can dramatically exaggerate flow disturbances and enhance the diagnostic sensitivity of color flow mapping. Thus, DCFM has been established as a sensitive technique for the assessment of blood flow in both surgical and nonsurgical patients.

The incorporation of DCFM in a transesophageal imaging system facilitates its use in the operating room for the intraoperative evaluation of anatomic lesions and surgical repairs; it also becomes available to the anesthesiologist to guide hemodynamic management. For example, the effects of vasoactive drugs on valvular regurgitation or intracardiac shunting can be seen instantaneously. This will be particularly helpful in the patient with congenital heart disease. Our initial experience with this technique suggests that it will be relatively easy to learn, although a number of validation studies need to be done. In particular, quantitative evaluations of flow are needed. Several investigators (6,8) have noted that the linear dimensions of regurgitant flow, for example, generally correlated with the severity of regurgitation by cineangiography. In our own experience, several patients, including the three patients undergoing CABG, showed some degree of mitral regurgitation; this may not always be clinically significant. It has previously been reported that regurgitation through a 1-mm orifice can be detected by DCFM (8). In addition, the technique allows the spatial orientation of flow to be determined. In two patients we observed evidence of blood flow originating from the site of surgical repair: in one patient this suggested a paravalvular leak at the mitral valve annulus and in another patient repair of the interatrial septum was followed by the development of a small right-to-left shunt.

Small leaks along suture lines may prove to be frequent occurrences detectable by DCFM but of little clinical significance. However, with experience, surgically unacceptable repairs may be identified and corrected promptly, to the benefit of the patient.

The phenomenon of color reversal or frequency aliasing may confuse the color display. Further technical refinements can be expected to reduce the problem of aliasing. Because color is derived from the direction and velocity of blood flow relative to the transducer, it should be emphasized that normal and abnormal flow must be described in relation to a specific two-dimensional view; imaging in the opposite direction would result in an exactly opposite color display. We have also noted that color signals may be derived from slow-moving cardiac structures, such as the tricuspid valve at end diastole moving towards the transducer. With experience the linear color signal following the valve can be distinguished as a "ghost signal" derived from a cardiac structure rather than blood flow.

The development of TEDCFM holds considerable promise for the understanding of blood flow in normal and pathologic conditions, which will find clinical application in the management of patients under the care of anesthesiologists.

Hewlett-Packard kindly provided us with a prototype transesophageal ultrasound transducer and a color flow mapper at a time when they were not yet available for worldwide distribution.

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1987;66:391–4

Effects of U-50488H, a Selective κ-Analgesic, on the Minimum Anesthetic Concentration (MAC) of Halothane in the Rat

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ALTHAUS JS, VON VOIGTLANDER PF, DI FAZIO CA, MILLER ED. Effects of U-50488H, a selective κ-analgesic, on the minimal anesthetic concentration (MAC) of halothane in the rat. Anesth Analg 1987;66:391–4.

The effects of U-50488H, a selective κ-analgesic, on the minimum anesthetic concentration (MAC) of an inhalational agent (halothane) were studied in the rat. U-50488H was given subcutaneously in doses of 3, 10, and 30 mg/kg body weight. The maximal MAC reduction was about 60%. The potency ratio of U-50488H to morphine in this model was comparable with potency ratios in other analgesic assays. In separate experiments, the percent reduction in halothane MAC with U-50488H at 30 mg/kg was determined during the infusion of naloxone (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 1 $mg \cdot kg^{-1} \cdot min^{-1}$) at doses shown to have reversed a 70% reduction in MAC by 10 mg/kg of morphine. Only when naloxone was infused at 1 $mg \cdot kg^{-1} \cdot min^{-1}$ was there a significant reversal of the U-50488H-induced reduction in halothane MAC. This observation suggests that the reduction in MAC of halothane with U-50488H was not mediated by a μ-receptor. In conclusion, through the use of a selective pharmacologic tool that stimulates κ-receptors we have demonstrated potential utility of κ-analgesics as supplements to general anesthesia.

Key Words: ANALGESICS—U-50488H. POTENCY, ANESTHETIC—MAC. ANESTHETICS, VOLATILE—halothane.

U-50488H is a selective and structurally novel non-μ-opioid agonist. It has effective analgesic properties comparable with morphine but, in contrast, it acts selectively through κ-opioid receptors. Having minimal side effects of respiratory depression and muscle rigidity and low abuse potential, U-50488H may be useful as a supplement to general anesthesia with inhalational agents. The purpose of this study was to determine the anesthesic potency of κ-analgesics as measured by the changes in the minimum anesthetic concentration (MAC) of halothane with increasing doses of U-50488H.

Methods

The animals involved in this study were cared for and used in accordance with the Guide for the Care and Use of Laboratory Animals, DHEW Publication (NIH) 85-23, 1985 and the Animal Welfare Act. Halothane MAC and changes in halothane MAC with U-50488H were determined in 11 Sprague-Dawley rats, weighing between 280 and 390 g, as described previously (1). Each rat was placed in a clear plastic cone and anesthetized with 3.5% halothane and oxygen for 3–5 min. Tracheal intubation was accomplished with a 16-gauge polyethylene catheter. Halothane concentration was reduced to 1.5%, and the rat was allowed to breathe spontaneously until cannulation of a femoral artery and vein with PE50 tubing was accomplished. Halothane concentration was then decreased further to 1.25%, and ventilation was controlled with a Harvard animal respirator, using measurement of arterial blood gases to maintain normal Po_2, Pco_2, and pH. The arterial line was connected to a Statham P23Db pressure transducer used to continuously monitor systolic and diastolic blood pressure and heart rate on a Grass Polygraph 7 recorder. Colonic temperature was measured by a Yellow Springs thermister and maintained at normothermia with a heating blanket and lights.

A fine polyethylene catheter (PE10) was introduced through and beyond the endotracheal tube until obstruction to passage was noted, and was then withdrawn 1–2 mm. Gas samples for measurement of alveolar anesthetic concentrations were obtained by withdrawing 10 ml of gas through the catheter into glass syringes over 3–5 min at the time of tail-clamp

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Table 1. Effect of U-50488H Doses on Halothane MAC For Each Rat

Rat Number	MAC (% Halothane)	Dose (mg/kg)	Decrease (%)	Group decrease (Mean % ± SEM)
1	0.755	3	0	0 ± 0
2	1.235	3	0	
3	0.875	10	64.6	41.7 ± 8.6
1	0.755	10	44.9	
2	1.235	10	26.4	
4	0.840	10	31.0	
5	0.596	30	62.6	63.0 ± 5.5
6	0.868	30	47.8	
2	1.235	30	69.8	
7	1.070	30	59.5	
8	0.759	30	42.4	
9	0.835	30	81.0	
10	0.859	30	53.4	
11	0.817	30	87.4	

and were assayed using gas chromatography with a Hewlett-Packard model 5750 with flame ionization detector. A constant alveolar concentration of halothane was verified by analyzing triplicate samples. Control MAC levels were established according the method described (2) using a long hemostat clamped to full ratchet lock on the tail for 1 min. The tail was always stimulated proximal to a previous test site. Gross movement of the head, extremities, and/or body was taken as a positive test to stimuli whereas grimacing, swallowing, chewing, tail flick, or no response were considered negative. The halothane concentration was decreased in increments of 0.2 to 0.25%, until the negative response became positive, allowing about a 12 min equilibration after changes in concentration. MAC was considered to be the concentration midway between the lowest concentration associated with a negative response and the highest concentration that produced a positive response. After a control MAC was established, the halothane concentration was increased to 1.25%. U-50488H was then administered subcutaneously in doses of either 3, 10, or 30 mg/kg. Because the analgesic half-life of U-50488H given subcutaneously is about 50 min (unpublished data), supplemental quarter doses were given subcutaneously every 25 min. After the initial injection of each drug dose, 25 min was allowed to elapse before starting the MAC determination procedure. At this time the first supplemental dose was also given. The experiment continued an additional 30–45 min. Usually two different doses of U-50488H were tested per rat, beginning with the lower dose.

In six rats, naloxone was infused to determine if the reduction in halothane MAC by 30 mg/kg U-50488H could be reversed. After MAC was determined with

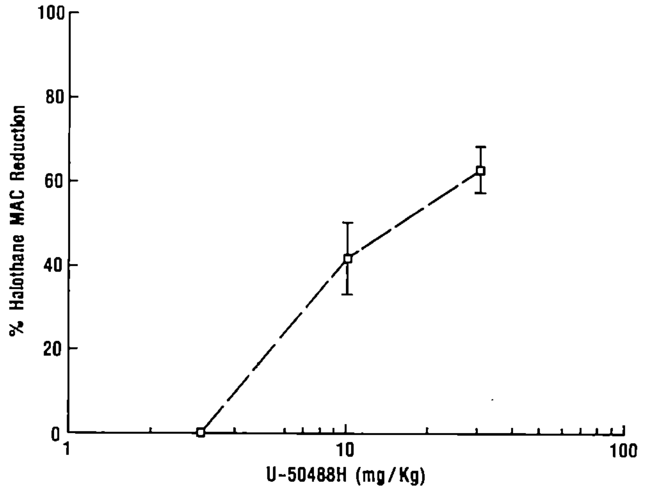


Figure 1. Effects of U-50488H on halothane MAC. Doses of U-50488H (3, 10, and 30 mg/kg) were given subcutaneously after the control levels of halothane MAC were determined for each rat. Thereafter quarter doses were given every 25 min until the completion of each experiment. The data are presented as mean % ± SEM. Control MAC values and the number of determinations at each dose are indicated in Table 1.

30 mg/kg of U-50488H and after a supplemental dose was given, halothane MAC was redetermined while naloxone was being infused continuously (for not more than 45 min) at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This was then repeated while naloxone was being infused continuously (for not more than 45 min) at 1 $mg \cdot kg^{-1} \cdot min^{-1}$. Statistical differences in halothane MAC were determined between a group receiving 30 mg/kg of U-50488H and groups receiving 30 mg/kg of U-50488H during naloxone infusion. $P \leq 0.05$ was considered significant by Bonferroni's unpaired *t*-test (3).

Results

The control MAC for halothane from 11 rats was 0.88 ± 0.07 (mean ± SEM), which was in agreement with previous results (1,2). In Table 1, reductions of halothane MAC are listed for three doses of U-50488H tested (3, 10, and 30 mg/kg). The results are reasonably consistent within each group, although at 10 mg/kg the standard error was more than 20% of the mean. This may reflect the greater potential for variance at this point on the dose-response curve. In Figure 1, the results from Table 1 are illustrated as a semilogarithmic plot of percent halothane MAC reduction vs dose of U-50488H. The shape of the curve suggests a response over a narrow dose range. It also suggests a decreased rate of change in the percent reduction in MAC with U-50488H at 30 mg/kg. The percent reduction in MAC was never greater than 87.4% at 30 mg/kg in eight determinations.

Table 2. Naloxone Reversals of Halothane MAC Reduction with-U-50488H (30 mg/kg) For Each Rat

Rat Number	MAC (% Halothane)	Naloxone ($\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$)	Decrease (%)	Group decrease (Mean % ± S.E.M.)
1	0.759	0	42.4	62.4 ± 7.5
2	0.835	0	81.0	
3	0.859	0	53.4	
4	0.817	0	87.4	
5	0.596	0	62.6	
6	0.868	0	47.8	
1	0.759	5	54.3	48.3 ± 5.0
3	0.859	5	56.6	
5	0.596	5	48.0	
6	0.868	5	34.2	
2	0.835	1000	15.0	11.0 ± 4.5
4	0.817	1000	21.9	
5	0.596	1000	2.0	
6	0.868	1000	5.3	

In Table 2, reductions in halothane MAC with U-50488H at 30 mg/kg are listed for three infusion rates of naloxone at 0, 5 and 1000 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ as determined in six rats. As illustrated in Figure 2, 5 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ had no significant effect on the reduction of halothane MAC produced by 30 mg/kg of U-50488H. On the contrary, at 1 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$, naloxone almost completely reversed the effects of U-50488H. In a single experiment, 10 mg/kg of morphine produced a 75% reduction in halothane MAC. When naloxone was infused at either 5 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ or 1 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$, 10 mg/kg of morphine produced at most only a 5% reduction in halothane MAC. Blood gas tensions were maintained within a normal range during the course of each experiment and there was no evidence of muscle rigidity even at the highest levels of MAC reduction.

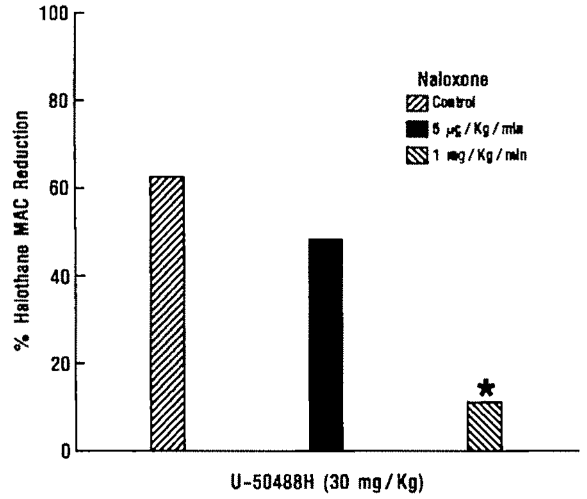
Discussion

Reduction in the anesthetic requirement of halothane by narcotics has been studied extensively in the same model used in our study (1,4,5). The dose-response effect of morphine on halothane MAC was shown to be hyperbolic in shape and was approaching saturation at about 80% MAC reduction. The dose-response effects of sufentanil and alfentanil on halothane MAC were sigmoidal in shape approaching a peak effect of greater than 90% MAC reduction with sufentanil. Maximal response with alfentanil was unattainable because side effects of muscle rigidity prevented accurate measurements above infusions of 15 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$. Although used successfully in the clinical setting to supplement inhalational agents, each narcotic mentioned earlier is not without its own inherent problems when used for this purpose. Complications related to cardiovascular instability (6), respiratory depression (7), and muscle rigidity (1) make μ-receptor mediated narcotics less than ideal.

The narcotic agonist-antagonists are a recently developed novel class of drugs. Their clinically desirable properties stem from the fact that they are μ partial agonists and have varying degrees of κ-agonist properties. One such drug, nalbuphine, does not display the severity of respiratory side effects typical of μ-agonists. Unfortunately, in the same rat model studied here, nalbuphine never decreased the MAC of halothane by more than 20% (5).

U-50488H is a structurally novel non-μ-opioid agonist believed to interact selectively with a κ-opioid receptor (8–10). This compound displays analgesic actions in a variety of assays (thermal, pressure, and irritant) in mice and rats. In most of these assays, U-50488H is nearly as potent as morphine. Other pharmacologic data suggest that the κ-opioid analgesia exhibited by U-50488H is dependent on serotonergic mechanisms (11). Interestingly, the anesthetic potency of sufentanil in our rat model is partially antagonized by para-chlorophenylalanine at concentrations known to deplete serotonin centrally by 70% (12).

Several of the properties of selective κ-receptor agonists such as respiratory and cardiovascular stability and low abuse potential make drugs such as U-50488H potentially useful clinically. For this reason, anesthetic interactions of U-50488H with an inhalational anesthetic were studied. The reductions in halothane MAC by U-50488H at 30 mg/kg were comparable with the effects of morphine at 10 mg/kg (1). This ratio in potency was similar to other assays of analgesia, but the absolute ED_{50} values from these other assays were approximately 10 fold less than was the dose of mor-



*$p < 0.05$ by unpaired t test.

Figure 2. Effect of naloxone on the reduction in halothane MAC produced by 30 mg/kg of U-50488H. Naloxone was infused at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and at 1 $mg \cdot kg^{-1} \cdot min^{-1}$ as described in METHODS. Data are presented as mean % ± SEM. Control MAC values and the number of determinations at each dose of naloxone are indicated in Table 2. When rats receiving both 30 mg/kg of U-50488H and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of naloxone are compared by unpaired t-testing to rats receiving only 30 mg/kg of U-50488H, the difference in halothane MAC was not significant ($P = 0.1996$). When rats receiving both 30 mg/kg of U-50488H and 1 $mg \cdot kg^{-1} \cdot min^{-1}$ of naloxone are compared by unpaired t-testing to rats receiving only 30 mg/kg of U-50488H, the difference in halothane MAC was significant ($P = 0.0009$).

phine or U-50488H required to reduce halothane MAC by 50%. This may be related to the relative insensitivity of the test used here, which uses a strong nociceptive stimulus and requires a well directed response.

Much of the pharmacologic evidence demonstrating the non-μ selectivity of U-50488H results from studies involving the use of narcotic antagonists (8). These studies utilized naloxone and MR-2266 as relatively selective opioid antagonists for μ and κ receptors, respectively. The results showed that MR-2266 was more effective in reducing U-50488H analgesia than morphine analgesia, whereas naloxone was much more effective in reducing morphine analgesia than U-50488H analgesia (8). In the context of our data, naloxone infused at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not significantly reverse the effects of U-50488H. However, this dose did reverse a similar level of MAC reduction induced by morphine. Naloxone at 1 $mg \cdot kg^{-1} \cdot min^{-1}$ was able to reverse the effects of both U-50488H and morphine. This suggests that the reduction in halothane MAC observed with U-50488H may be mediated by a non-μ opioid receptor.

In conclusion, through the use of a selective pharmacologic agonist of κ-receptors we have demonstrated a potential utility of κ-analgesics as supplements to general anesthesia.

U-50488H, trans-(-)-3,4-dichloro-N-methyl-N—2-(1-pyrrolidinyl) cyclohexyl-benzeneacetamide methane sulfonate hydrate was synthesized by Dr. J. Szmuszkovicz of The Upjohn Company.

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1987;66:395–400

Epinephrine Improves the Quality of Spinal Hyperbaric Bupivacaine for Cesarean Section

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ABOULEISH EI. Epinephrine improves the quality of spinal hyperbaric bupivacaine for cesarean section. Anesth Analg 1987;66:395–400.

In a double-blind randomized study, the effects of the addition of epinephrine on hyperbaric spinal bupivacaine were studied in 63 patients having elective repeat cesarean sections. In the study group (32 patients), the addition of 0.2 mg epinephrine improved the quality of analgesia since fewer patients required supplementation of the spinal anesthetic; the motor block was more profound; and the times to two-segment regression, sensory recovery, and motor recovery were prolonged.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—obstetric.

There is general agreement that epinephrine prolongs the duration of sensory and motor blockade when added to spinal tetracaine (1–4). No such agreement exists, however, with respect to the effect of epinephrine when given with spinal bupivacaine or lidocaine. Chambers and associates (5) and Spivey (6) found that the addition of epinephrine to spinal lidocaine only prolonged the recovery of both motor and sensory functions, but neither study showed improved quality of analgesia or motor paralysis or differences in the dermatomal levels of the sensory block associated with the use of epinephrine. The authors concluded that epinephrine did not serve a clinically useful purpose when added to lidocaine spinal anesthetics. On the other hand, Leicht and associates found that the addition of epinephrine significantly prolonged both the time for two-segment anesthesia regression and the duration of sensory and motor blockade (7). Animal studies have shown that, with spinal lidocaine, epinephrine increases the dermatomal level of anesthesia and prolongs sensory and motor block in monkeys (8), and in dogs is associated with a 46% increase in the duration of motor block (9).

Studies concerning the effects of epinephrine with spinal bupivacaine are limited and controversial. Moore found that epinephrine caused a more rapid onset of anesthesia, a longer time for two-segment regression to occur, more intense motor paralysis, and prolonged sensory and motor blockade (2). On the other hand, Chambers and associates found that the addition of epinephrine did not change the time of onset of anesthesia, the intensity of the anesthesia, or the time required for two-segment regression; epinephrine prolonged only the time required for complete recovery from the block (10). They concluded that epinephrine served no useful purpose with bupivacaine spinal anesthetics.

Because of this controversy, we performed this prospective double-blind, randomized study of a large number of unpremedicated patients of similar age and physical status, having the same surgical procedure at the term of pregnancy, all with intact fetal membranes, and none in labor.

Methods

The study involved 63 term ASA I patients not in labor who were scheduled for elective repeat cesarean section under spinal anesthesia. None of the fetuses had antenatal evidence of distress or compromise. After giving their consent, patients were randomly divided into two groups. In the study group (32 patients), 0.2 mg epinephrine was added to bupivacaine, whereas in the control group (31 patients), no additive was used. The anesthetic was 0.75% bupivacaine hydrochloride in 8.25% dextrose, a hyperbaric solution hav-

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ing a specific gravity of 1.035 at 25°C and 1.030 at 37°C. The dose was calculated according to each patient's height, with administration of 8.25 mg (1.1 ml) for a 150-cm patient—the dose increased or decreased by 0.1 mg bupivacaine for each 1-cm variation above or below that height. No premedication was administered. The spinal anesthetic technique was the same in all the patients. Lactated Ringer's solution, 15 ml/kg, was infused intravenously over 20 min before injection of the local anesthetic into the subarachnoid space. Spinal anesthesia was induced with the patient in the right lateral horizontal position. Lumbar puncture was performed at the L2–3 interspace using a 26-gauge spinal needle. Free flow of clear cerebrospinal fluid before and after injection of the local anesthetic was mandatory for inclusion in the series. This ensured proper placement of the injectate into the subarachnoid space.

The intrathecal injection of the local anesthetic was completed in 10 sec. Immediately after the injection, the patient was gently turned to the supine horizontal position, which was maintained for at least 20 min. Left uterine displacement was accomplished using an air bag (11). Arterial blood pressure and heart rate were monitored noninvasively using an automatic oscillotonometric device (Dinamap®) cycling every 30 sec to 1 min until the delivery, and every 2 min thereafter. The heart was also monitored using a precordial stethoscope and ECG. Hypotension was defined as a 20% decrease in systolic blood pressure. Ephedrine, injected IV in 10-mg increments, was used to correct maternal hypotension. Oxygen at a flow rate of 4 L/min was administered through a plastic face mask or nasal cannulae, depending on the patient's preference. Morphine in 2.5 mg IV increments was used to treat anxiety, discomfort, or pain after delivery. If the block appeared to be inadequate, or if 15 mg of morphine was unsuccessful in controlling pain, the patient was given general anesthesia using endotracheal intubation following a rapid sequence induction.

The times of bupivacaine injection, start of surgery, delivery, and termination of surgery were recorded. Since the block was administered with the patient in the right lateral position, the onset and spread of the block were expected to occur earlier on the right side. Therefore, in all patients, the dermatomal level of sensory anesthesia was tested by pinprick 7.5 cm from the midline on the right side, at 2 min, 5 min, 10 min, 15 min, and 20 min after the spinal injection. At the same times, motor power was also assessed on the right side, using the Bromage scale for motor function [0, patient able to move her entire right lower extremity; 1, unable to flex hip; 2, unable to flex hip and knee; 3, complete motor blockade of the lower limb (12)]. Time to two-segment regression of the level of sensory anesthesia was also determined by pinprick every 30 min on the right side. Time to complete sensory and motor recovery was determined by return of sensation to all the body and free movement of both lower limbs. The degree of analgesia was arbitrarily rated "excellent" if no supplementation was required; "very good" if morphine was required in amounts of 5 mg or less; "good" if the amount of morphine needed was more than 5 mg and less than 10 mg; and "poor" if the amount of morphine exceeded 10 mg or if general anesthesia was required.

The author prepared the injectate and gave the anesthesia or supervised its administration. An anesthesia resident collected the data, a neonatologist evaluated the neonate, and neither the physicians evaluating the technique nor the patient knew the nature of the injectate. The data were analyzed by an independent statistician. For statistical analysis, numerical variables (e.g., age, weight, dermatomal level) were compared using a two-sample *t*-test. When using a categorical variable (e.g., degree of analgesia), a χ^2 test was performed; a *P* value of less than 0.05 was considered statistically significant. Data are expressed as mean ± standard error of mean (SEM).

Table 1. Thoracic Dermatomal Level of Sensory Anesthesia after Spinal Injection of Bupivacaine

Time after injection (min)	Study group (n = 32)	Control group (n = 31)
2	6.7 ± 0.4	6.1 ± 0.5
5	4.2 ± 0.3	4.2 ± 0.4
10	2.7 ± 0.3	3.0 ± 0.4
15	2.6 ± 0.3	2.8 ± 0.4
20	2.6 ± 0.3	2.8 ± 0.4

Mean ± SEM. No significant differences.

Results

The two groups were comparable in terms of age, height, weight, gestational age, parity, and gravidity. The doses of bupivacaine injected into the subarachnoid space in the two groups were similar (9.3 ± 0.1 mg in the study group or the control group). The rate of spread of anesthesia after injection was similar in both groups (Table 1). There was also no significant further spread of the sensory level after 10 min in either group (Table 1). The Bromage scores were higher in the study group than in the control group at 2, 5, 10, and 15 min but not at 20 min (Fig. 1). One patient

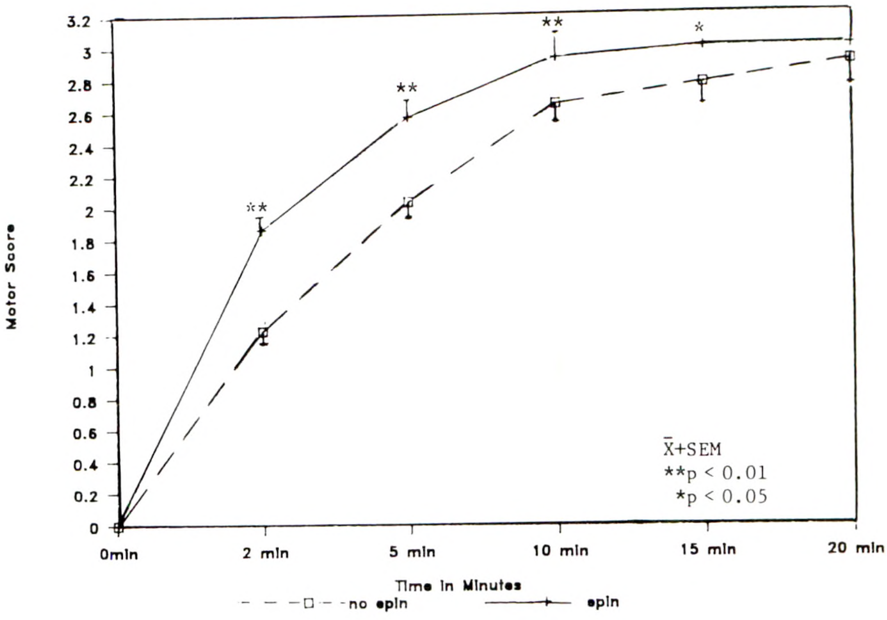

Figure 1. Effect of epinephrine on Bromage motor score using spinal bupivacaine.

Table 2. Rating of Analgesia and Supplementation of the Spinal Anesthetic

Study group	n = 32 (100%)	Reason for supplementation	Relation to delivery
Excellent (no supplementation)	25 (78%)	—	—
Very good (≤5 mg morphine)	6 (19%)	Anxiety, discomfort on abdominal manipulations, and/or pulling on uterus	After
Good (>5–10 mg morphine)	0 (0%)	—	—
Poor	1 (3%)		
(>10 mg morphine)	0	—	—
(general anesthesia)	1	Pain	Before
Control group	n = 31 (100%)		
Excellent (no supplementation)	14 (45%)	—	—
Very good (≤5 mg morphine)	5 (16%)	Anxiety, discomfort on abdominal manipulations and/or pulling on uterus	After
Good (>5–10 mg morphine)	10 (33%)	Discomfort on abdominal manipulations, pulling on peritoneum, pulling on uterus, freeing adhesions, and/or pulling on omentum	After
Poor	2 (6%)		
(15 mg morphine)	1	Pain with abdominal manipulations	After
(15 mg morphine and general anesthesia)	1	Pain with abdominal manipulations and pulling on uterus	After

Significant difference between the two groups ($P < 0.05$).

in the study group and three in the control group had incomplete motor paralysis (no statistical difference).

The quality of analgesia significantly improved with the addition of epinephrine (Table 2). In the study group, 97% of the patients had "excellent" or "very good" analgesia compared with 61% in the control group ($P < 0.05$). There was no difference between the two groups regarding the incidence of maternal hypotension, nausea, or vomiting, or the frequency with which ephedrine was required to correct hypotension or the dose of ephedrine used (Table 3). Times for two-segment regression, motor recovery, and sensory recovery were all significantly longer in the study group (Table 4). The fetal outcomes as eval-

Table 3. Hypotension, Nausea, Vomiting, and Ephedrine Dosage

	Study group (n = 32)	Control group (n = 31)
Ephedrine dose (mg, mean ± SEM)	20.8 ± 3.0	19.0 ± 2.8
Hypotension (incidence)	50%	54%
Nausea (incidence)	43%	40%
Vomiting (incidence)	32%	35%

No significant differences.

Table 4. Recovery from Anesthesia (Min)

	Study group (n = 32)	Control group (n = 31)
Two-segment regression	90.1 ± 4.4[a]	75.7 ± 3.2
Complete sensory regression	186.8 ± 8.7[b]	155.8 ± 9.3
Complete motor regression	167.8 ± 7.9[b]	141 ± 5.8

Mean ± SEM; [a]$P < 0.01$; [b]$P < 0.05$

uated by the Apgar scores were similar; 1-min scores in both groups were between 7 and 9, and the 5-min score between 8 and 10.

Discussion

Our results show that the addition of epinephrine improves the quality of the spinal anesthetic produced by bupivacaine since the analgesia was better, motor blockade was complete and developed more rapidly, and the duration of the block was prolonged. However, the prolongation of recovery from the spinal block in the study group by 30 min over the control group may be a disadvantage in a busy unit. Our findings, in general, agree with those of Moore (2) and disagree with those of Chambers and associates (10). The difference between our findings and those of Chambers and associates may be explained by the small number of their study subjects (ten in each group) (10,13).

In our study, the onset and the extent of the sensory block were similar in both groups and did not significantly change after 10 min. However, caution should be exercised in changing the operating table from the horizontal to the Trendelenburg position within 20 min of administration of this or other types of hyperbaric spinals because occasionally the level of sensory, motor, or sympathetic block may unnecessarily extend cephalad to high, and potentially dangerous, levels.

In the present study, unequal volumes of injectate were, of course, used in the two groups since 0.2 ml of epinephrine solution was added to that of the study group and nothing to that of the control group. Spivey added saline to the local anesthetic in the control group to ensure that volumes remained constant (6). We chose to have an experimental design similar to the usual clinical practice. Moreover, such a small (0.2 ml) difference in volume does not affect the quality of the block; 30 mg spinal lidocaine in 0.6 ml or in 1.5 ml produces the same level of anesthesia (8).

Our results show an apparent difference between the effects of epinephrine on the rate of spread of the sensory and motor blockade. In comparing Figure 1 with Table 1, it appears as if epinephrine enhanced the rate of the motor spread, as indicated by higher Bromage scores, whereas there was no difference in the rate of the sensory spread. However, the Bromage scoring system indicates complete paralysis of certain muscle groups and does not take into account their paresis. Accordingly, the higher Bromage scores in the study group only indicate that epinephrine caused *paralysis* to occur earlier than in the control group, and not necessarily a more rapid spread of the motor blockade.

How epinephrine intrathecally injected affects the action of local anesthetics used for spinal anesthesia remains unclear. The classic theory is that epinephrine causes vasoconstriction, thus delaying the absorption of the local anesthetic drug. However, this theory has been refuted with both tetracaine and lidocaine. With the former, Converse et al. found that despite the prolongation of spinal tetracaine by the addition of epinephrine, the cerebrospinal levels of tetracaine were independent of epinephrine injection (14). With lidocaine, Denson et al., in monkeys (8), and Ravindran et al., in dogs (9), found that the pharmacokinetics of lidocaine after its intrathecal injection were not altered by the addition of epinephrine, despite prolongation of the block. For example, in arterial blood samples, the time to peak plasma concentration of lidocaine injected into the subarachnoid space and the area under the plasma concentration–time curve from zero to infinity (AUC 0–∞) were independent of epinephrine (8). There was also no correlation between lidocaine arterial plasma level and the degree of motor blockade (9). In humans, Axelsson et al. found that addition of epinephrine to lidocaine decreased lidocaine blood levels (15). However, they measured venous, not arterial, blood levels. Kozody et al., in a study of dogs to identify the effect of epinephrine alone or in combination with local anesthetics on the spinal cord blood flow (SCBF), found that epinephrine alone, 200 μg, did not change SCBF (16). Tetracaine alone caused vasodilation in the lumbosacral region. The addition of epinephrine counteracted this vasodilation (17). Bupivacaine, on the other hand, caused vasoconstriction in the lumbosacral region that was unaltered by the addition of epinephrine (18). They postulated that epinephrine prolonged the anesthetic effect of tetracaine by counteracting the vasodilation, thus decreasing the absorption of the local anesthetic. With bupivacaine, the blood flow in the region where the drug had been injected intrathecally was not changed by the administration of epinephrine; therefore, any effect of epinephrine on the anesthetic properties of spinal bupivacaine could not be explained by changes in the SCBF.

The second possibility is that the addition of epinephrine changes the pH of the local anesthetic solution to be injected. Following this study, we measured the pH of three solutions: 0.75% bupivacaine in 8.25% dextrose; 1:1000 epinephrine; and a combination of 1.2 ml of 0.75% bupivacaine in 8.25% dextrose with 0.2 ml of a 1:1000 epinephrine solution. The pH values were 5.16, 3.29, and 4.27, respectively. The difference in pH in a small volume of injectate will be of little consequence when diluted by the large volume of the cerebrospinal fluid, which has a high pH value, especially in the term pregnant patient (20). Moreover, the addition of epinephrine lowers the pH of the injectate, and if it does anything, it impedes the diffusion of the local anesthetic through neural membranes by decreasing the undissociated fraction of the drug. Thus, latency would be expected to be increased with the addition of epinephrine (21), which we did not find. Accordingly, it is unlikely that the change in pH by the addition of epinephrine was responsible for improving the quality of the motor and sensory properties.

The third possible mechanism of action of epinephrine in affecting responses to local anesthetic solutions used for spinal anesthesia is a direct effect on neural tissues. Collins and associates, in using the decerebrate spinal cord-transected cat model, found that epinephrine suppressed noxiously evoked activity in a wide dynamic range of neurons in the dorsal horn of the spinal cord (22). Therefore, the augmentation of the sensory blocking effects of spinal bupivacaine by the addition of epinephrine may include a direct nociceptive blocking effect by epinephrine. The increase in the degree of the motor paralysis of bupivacaine produced by epinephrine in this study is difficult to explain. Could it have been due to a direct effect on the motor nerve roots, the anterior horn cells, and/or the descending tracts? This interesting facet of epinephrine action warrants further investigation.

In conclusion, epinephrine improves the sensory and motor quality of hyperbaric bupivacaine spinal anesthesia in cesarean section.

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Comparison of Continuous Epidural Infusion of a Local Anesthetic and Administration of Systemic Narcotics in the Management of Pain after Total Knee Replacement Surgery

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RAJ PP, KNARR DC, VIGDORTH E, DENSON DD, PITHER CE, HARTRICK CT, HOPSON CN, EDSTRÖM HH. Comparison of continuous epidural infusion of a local anesthetic and administration of systemic narcotics in the management of pain after total knee replacement surgery. Anesth Analg 1987;66:401–6.

Continuous bupivacaine epidural analgesia was compared with conventional methods of systemic analgesic administration in the management of postoperative pain in 30 patients for 3 days following total knee replacement surgery. Patients given continuous epidural analgesia had significantly better pain relief (visual analogue scale, global evaluation), needed significantly fewer supplementary analgesics, and had significantly fewer side effects. In the epidural group, sensory block averaged six dermatomes on day 1 and four dermatomes on day 3. The number of patients with complete (or almost complete) motor block of the lower limbs decreased from eight on day 1 to five on day 3. The mean dosage of bupivacaine decreased from 21.0 ± 5.7 (SD) mg/hr on day 1 to 15.1 ± 8.5 mg/hr on day 3. No signs of accumulation of or toxic reactions to bupivacaine were seen.

Key Words: ANESTHETIC TECHNIQUES—epidural. PAIN—postoperative.

In the current clinical practice, the quality of analgesia for postoperative pain relief is still inadequate. This is partly due to the fact that the intensity of pain is extremely variable not only among patients, but also with different surgical procedures. Often, however, inadequate pain relief is the result of poorly conceived prescribing formulas (1) and/or inconsistent administration of prescribed analgesics (2–4). Often an attempt is not even made for optimal use of new, potent analgesics (5,6) and new techniques. This is reflected in the high proportion of patients (40–75%) who experience moderate or severe pain following surgery (1–3).

Although postoperative pain relief can be achieved by a number of techniques, such as intravenous administration of narcotics (7,8), patient-controlled analgesia (9), intermittent or continuous neural blockades with or without narcotics, transcutaneous electrical nerve stimulation (TENS), nitrous oxide, and cryoanalgesia, little effort has been made to compare various drug combinations and routes of administration in terms of effective postoperative analgesia under clinical conditions.

The aim of the present study was to compare continuous bupivacaine epidural analgesia with conventional methods of systemic analgesic administration for postoperative pain relief following total knee replacement surgery.

Methods

Material

The study was approved by the Institutional Review Board of the University of Cincinnati. Thirty patients scheduled for total knee replacement surgery were included in this study. They were assigned to one of two groups for postoperative pain relief in the following way. Patients were assigned to the two groups after they had selected either a general anesthetic or an epidural for their surgery. This decision was made in concert among the anesthesiologist, the surgeon, and the patient. Group I ($n = 15$) received conventional parenteral narcotics; group II ($n = 15$) received

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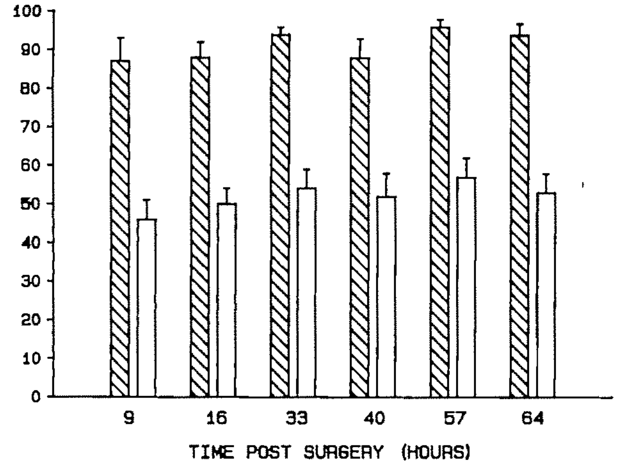

Figure 1. Relief of pain at different time intervals after analgesics in surgery (hatched bars = epidural group, open bars = conventional group). Epidural group was significantly better ($P < 0.001$) at all times postoperatively.

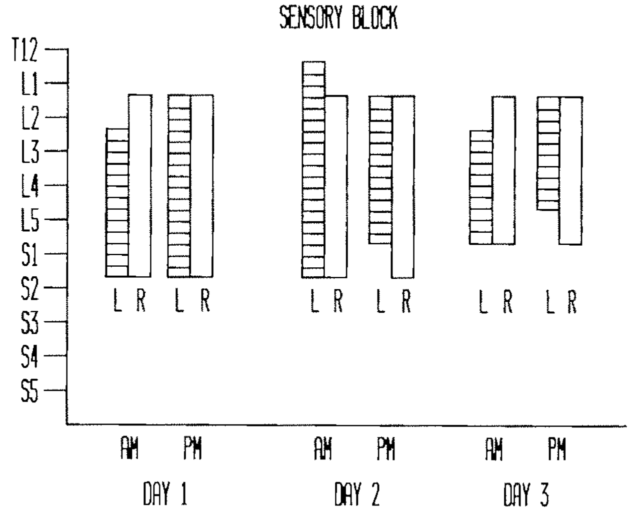

Figure 2. Sequential spread of analgesia to pinprick in the epidural group.

a continuous infusion of bupivacaine via a lumbar epidural catheter for management of postoperative pain. Patients were informed of the method of evaluation that would follow their surgery. All patients had a preoperative diagnosis of rheumatoid or degenerative arthritis and all, except for one in each group, had unilateral total knee replacement.

In group I, all patients had general anesthesia for surgery. After surgery, postoperative pain management was accomplished with conventional systemic administration of analgesics as prescribed by the orthopedic service. No restrictions were placed as to drug or frequency. The only narcotic analgesics prescribed for patients in the present study were morphine and meperidine.

Patients in group II (continuous epidural) had lumbar catheters placed prior to surgery and anchored for prolonged infusion. Choice of local anesthetic for surgery was left to the anesthesiologist and included bupivacaine, etidocaine, 2-chloroprocaine, lidocaine, or mepivacaine. In the immediate postoperative period, catheters were connected to a volumetric infusion pump for continuous delivery of bupivacaine. Infusions were started with 0.25% bupivacaine at an infusion rate of 6–15 ml/hr. The rate required to block six to eight dermatomes was determined by the height and weight of the patient as previously reported (10). Parenteral analgesics were used to supplement the epidural technique as necessary. At the termination of the study, the catheter was removed and the catheter tip and site of insertion were cultured.

All patients were evaluated for 3 days postoperatively. The pain relief, physiological changes, and side effects were monitored throughout and assessed twice daily by a research nurse (D.K.). Pain relief was scored using a standard visual analogue scale (VAS) from 0 (no pain relief) to 100 (complete pain relief). The clinical research nurse explained the VAS to the patients on the initial visit and the patients were instructed how to grade their pain relief.

The sensory blockade was assessed using the pinprick method and was recorded as the number of dermatomes blocked. Motor function of the contralateral limb was assessed on a 0–3 modified Bromage scale (11), with 0 representing complete block and 3 representing no block. Evaluation was restricted to the contralateral side due to immobilization of the surgical extremity or use of a continuous passive motion machine.

A list of potential side effects of the techniques was prepared and the patients reviewed their subjective side effects at the time of initial evaluation. The list included hypotension, nausea, vomiting, tingling under tongue, ringing in ears, convulsions, itching, urinary dysfunction, pyrexia, leucocytosis, headache, backache, feeling of coolness, constipation, diarrhea, decubitus, and tape irritation. Patients were instructed to report any additional side effects. Upon completion of the study, patients were also asked to grade the technique used for their pain relief. Global evaluation was scored from 0 to 3 (0 = no help, 1 = fair, 2 = good, and 3 = excellent).

In group II, a 5-ml venous blood sample was drawn from the patient daily. Plasma was separated by centrifugation as soon as possible and stored at 4°C. Bupivacaine plasma levels were measured by gas liquid

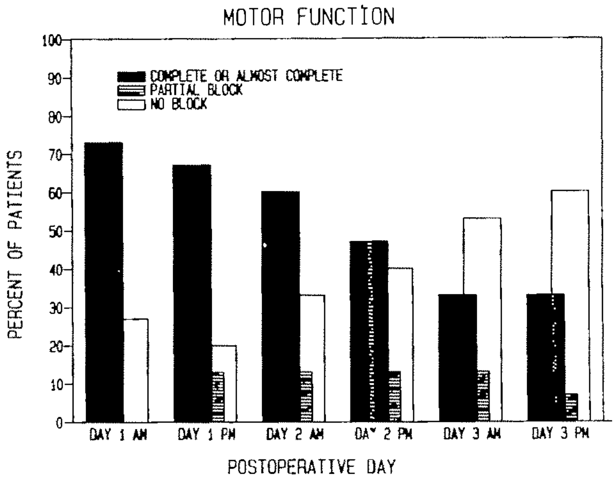

Figure 3. Distribution of degree of motor function of the lower limbs (epidural group) at different time intervals after surgery.

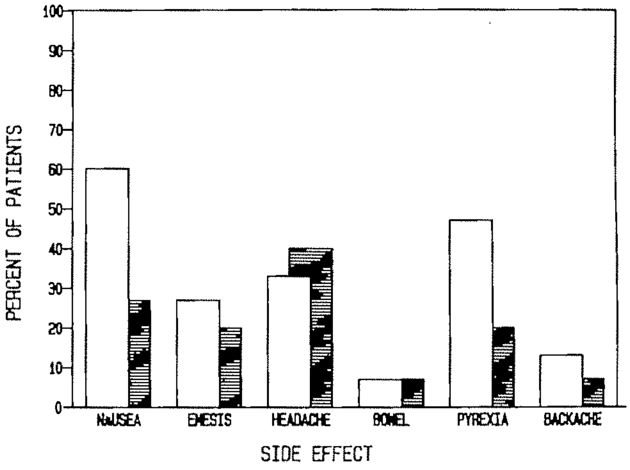

Figure 4. Frequency of adverse reactions on the first postoperative day (hatched bars = epidural group, open bars = conventional group). Nausea, emesis, pyrexia, and backache were significantly ($P < 0.05$) more frequent in the conventional group and headache was significantly ($P < 0.05$) more frequent in the epidural group.

chromatography according to the method of Coyle and Denson (12).

In both groups, usage of narcotic analgesics was recorded daily in terms of total dose and frequency of dosing per 24 hr. The only two narcotics prescribed in the present study were morphine and meperidine. Meperidine doses were converted to morphine equivalents.

All data are presented as means ± SD unless otherwise specified. Frequency distributions were tested by means of χ^2 with Yates continuity correction or Fisher's exact test. Differences between means were tested by Student's t-test. Regression analysis was performed with pain relief scores as the dependent variable and treatment group and time of observation (time of day postoperative) as the independent variable. Multivariate regression analysis was performed on each drug with dosage (mg/day) and frequency as the dependent variable and treatment group and day postoperative as the independent variables. In all cases, a $P < 0.05$ was considered the minimum level of statistical significance.

Results

Demographics

Mean age was similar in both groups: 61.3 yrs ± 15.6 (range 17–81) in group I, 66.3 yrs ± 13.2 (range 25–79) in group II. Race and gender were likewise similar in both groups. As measured by the VAS, group I patients reported 45–55% pain relief whereas group II patients reported 85–95% pain relief ($P < 0.001$; Fig. 1).

In group II, sensory block extended over a mean of six dermatomes on day 1, which receded to four dermatomes on day 3. Daily examination in group I showed no sensory block (Fig. 2). Complete or almost complete motor block was seen in eight of 15 group II patients on day 1. This decreased steadily so that by the third day only five of 15 patients had a complete or almost complete block. Patients in group I demonstrated no loss of motor function during the 3 days (Fig. 3).

Patients in group I had twice as many side effects as did patients in group II. More patients in group I had three or more side effects than in group II ($P < 0.01$). The incidence of nausea and vomiting was higher in group I. Foley catheters were inserted in 11/15 patients in group II intraoperatively or in the immediate postoperative period as a prophylactic measure. This precludes comparison of urinary dysfunction between groups.

The incidence of elevated temperatures (≥100°F) was greater in group I on postoperative days 1 and 2. Headache was experienced by five patients in group I and by eight patients in group II. Generalized itching was reported by two patients, both in group I. In two or fewer patients per group, hypotension, tape irritation, itching, and backache were seen (Fig. 4).

A significantly higher proportion (80%) of group II patients reported global scores of 3 (excellent) than did patients in group I ($P < 0.001$) (Fig. 5).

The mean dosage of bupivacaine decreased from 21.0 ± 5.7 (SD) mg/hr on day 1 to 15.1 ± 8.5 mg/hr on day 3 ($P < 0.05$). Mean plasma concentrations of bupivacaine on days 1–3 were 1.2 ± 0.8, 2.7 ± 0.9, and 2.1 ± 1.4 μg/ml, respectively.

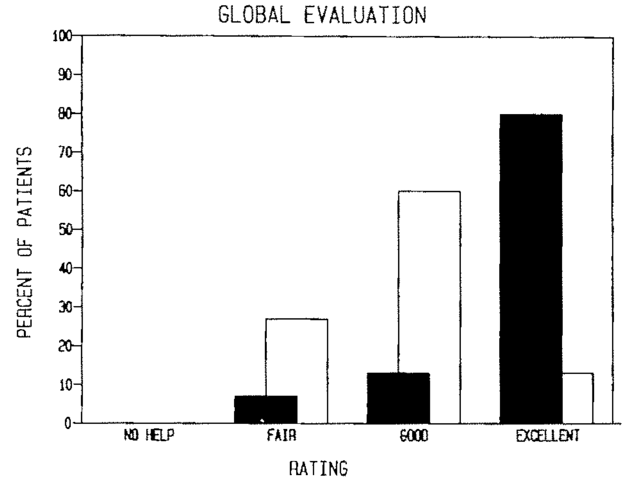

Figure 5. Distribution of global evaluation of the treatment (hatched bars = epidural group, open bars = conventional group). A significantly ($P < 0.001$) higher number of patients in the epidural group evaluated the treatment as excellent.

Table 1. Narcotic Use Postoperatively

	No narcotics	Narcotics	Total
Epidural	12 (80%)	3 (20%)	15
Conventional	2 (13.3%)	13 (86.7%)	15

$\chi^2_1 = 13.393$; $P < 0.005$.

The proportion of patients given narcotics was greater in group I than in group II ($P < 0.05$) (Table 1). These narcotics were also administered more frequently in group I, with a mean daily dosage of 24.7 mg (range 6–60 mg) compared with 12.2 mg (range 5–20 mg) in group II patients ($P < 0.05$).

Discussion

The relationship of the site of the surgery to the incidence of pain is roughly as follows: hip and other major joints, 30% moderate and 60% severe pain; upper intra-abdominal and thoracic, 40% moderate and 50% severe pain; lower intra-abdominal, 45% moderate and 35% severe pain; superficial operations on head, limbs, and chest wall, 35% moderate and 20% severe pain. In addition, the incidence and intensity of postoperative pain are influenced by personality, certain psychological factors (emotion and fear), and rapport of the patient with surgical, nursing, and anesthetic teams (13).

Pain that is inadequately treated intensifies reflex responses that can cause serious complications, such as pulmonary, intestinal, or urinary problems; thromboembolism; altered muscle metabolism; hyperdynamic circulation; and increased oxygen consumption (14). Following hip and knee surgery, the pain is associated with severe reflex spasm of the quadriceps, which further causes excruciating pain and impaired muscle function.

In the design of this study, postoperative pain due to knee replacement surgery was chosen as the model since 90% of the pain is moderate to severe. In addition, there is a requirement that patients start with continuous passive motion (by machine) in the immediate postoperative period. If pain relief by a particular technique is inadequate, the patient cannot participate in the rehabilitation program until better analgesia is provided.

Postoperative analgesia with systemic administration of narcotics on patient demand has long been the common method of pain relief. Its efficacy has been challenged, owing to inadequate dosage, delayed administration periods, and personal bias of those ordering and giving the analgesics (14). Even though regional anesthesia has been used for limb surgery, its potential benefit in a prolonged postoperative period has never been assessed and adequately compared with other postoperative analgesia techniques.

Epidural analgesia can be provided by intermittent or continuous infusion of local anesthetics. In the literature, comparisons have been made between the intermittent and continuous infusion techniques (15). Some believe that the intermittent technique is superior because of its simplicity, lack of cumulative effects, and adequate analgesia (16). Others believe that continuous infusion provides superior analgesia with fewer side effects and no tachyphylaxis (17). We chose the continuous infusion technique to compare with systemic administration of narcotics because of our previous experience and satisfaction with this technique.

In this study, group II (epidural) patients reported significantly ($P < 0.001$) higher pain relief scores (85–95%) than group I (systemic narcotics) patients (45–55%). This confirms the experiences of other workers who also reported that regional anesthesia provides superior postoperative analgesia when compared with other techniques (18). The patients in group II also had higher global scores than patients in group I.

As expected, the mean daily narcotic usage was greater in group I than in group II. We are puzzled as to why the patients in group II needed any systemic narcotics in the postoperative period if they had adequate analgesia with epidural bupivacaine. Perhaps personality traits and psychological factors come into play in acute pain states that compel some of the patients to be highly anxious and demand systemic medications. This factor, whether it is anxiety or pain, is not answered by this study.

Side effects common to both techniques were nausea, emesis, headache, bowel and urinary dysfunction, pyrexia, and backache. Urinary dysfunction could not be evaluated in this study since the majority of the patients were catheterized prophylactically by the Orthopedic Service. It was presumed by the surgeons that epidural bupivacaine would produce urinary retention if adequate analgesia were present. This may or may not be true. Another study will be done to answer this question. A higher incidence of nausea, emesis, pyrexia, and backache occurred in group I patients. A higher incidence of headache was found in group II patients. Nausea and emesis may be attributable to the narcotic administration and can be explained adequately on that basis. However, the increased incidence of pyrexia and backache in group I and headache in group II is surprising and needs further explanation. We hypothesize that pyrexia may be the result of increased metabolic rate as a postoperative sequela of surgical stress. In group I, the stress response was not suppressed adequately, whereas with the epidural local anesthetic administration in group II, the stress response was adequately suppressed.

Since the patients in this study underwent rigorous passive exercises of the operated extremity in the immediate postoperative period, it is understandable that backache could occur. Bupivacaine administered via the lumbar epidural route seems to be superior in preventing backache for such exercises. Headache can occur with systemic administration of either narcotics or local anesthetics. In the differential diagnosis, one can also think of cerebrospinal fluid leaks as a cause of headaches. We hypothesize that the increased incidence of headache as seen in group II patients may be due to absorption of local anesthetic (bupivacaine) into the epidural vessels, which then selectively traverses to the cranial vascular channels and produces vasodilation, and possibly headache. However, bupivacaine has been shown to produce dose-dependent vasoconstriction (19). Further studies are needed to confirm or deny this mechanism.

As expected, sensory and motor blocks were not seen in group I. In group II, numbness and motor weakness were proportional to the dose infused from day 1 to day 3. After effective analgesia was obtained on day 1, we found that the dose of the infused drug needed to be decreased to prevent further sensory loss and/or motor weakness. Tachyphylaxis was not a problem with continuous infusion of bupivacaine. Plasma bupivacaine concentrations in the steady state were below toxic levels in all group II patients. Thus, no evidence of accumulation of bupivacaine was seen in this study, as speculated in earlier reports (15,20).

Two patients in group II had significant complications. One patient had a small sacral decubitus, which was noticed on day 4. This could have been due to sacral pressure, most likely aggravated by sacral numbness. It clearly illustrates the need for careful inspection and care of desensitized areas. In the other patient, the epidural infusion was discontinued on day 4 and the patient then actively mobilized. While en route to the physical therapy department on the next day, he developed a sudden onset of shortness of breath and chest pain, became cyanotic, and expired during resuscitation attempts. Postmortem examination showed a massive pulmonary embolus. We believe that this could not have been prevented and possibly would occur in a certain percentage of patients undergoing knee surgery, and is unrelated to the analgesic technique.

Two patients in group I had significant complications. The first patient did well until the ninth postoperative day, when he developed right upper quadrant pain and anorexia. This was diagnosed as renal colic and required surgical intervention. The second patient could not increase his range of motion in the knee in the postoperative period and the knee had to be manipulated under general anesthesia 14 days after surgery.

In conclusion, this study compared the efficacy of continuous epidural infusion of bupivacaine with systemic narcotic agents for the management of pain following knee replacement surgery. Postoperative analgesia was superior with the continuous epidural infusion of bupivacaine and the incidence of side effects was less. Patients preferred the epidural technique to systemic narcotics.

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Bupivacaine Disposition in Mother, Fetus, and Neonate after Spinal Anesthesia for Cesarean Section

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KUHNERT BR, ZUSPAN KJ, KUHNERT PM, SYRACUSE CD, BROWN DE. Bupivacaine disposition in mother, fetus, and neonate after spinal anesthesia for cesarean section. Anesth Analg 1987;66:407–12.

Uptake of bupivacaine from the subarachnoid space and its placental transfer were measured in six patients undergoing elective cesarean section. Maternal plasma levels (59 ± 32 ng/ml) were only about 5% of those found in a comparable previous study of epidural anesthesia. Mean plasma umbilical venous bupivacaine levels (20.2 ± 21 ng/ml) were 7% of those found after epidural anesthesia. Mean umbilical venous/maternal venous bupivacaine ratios were 0.34 ± 0.12 and mean umbilical arterial/umbilical venous ratios were 0.81 ± 0.30. No bupivacaine was detectable in neonatal plasma 24 hr after delivery. Neonatal urine had measurable levels of both bupivacaine and its inactive metabolite, 2,6-pipecolylxylidine (PPX), for at least 36 hr after delivery. The results demonstrate that bupivacaine crosses the placenta and reaches the fetus, but in very low amounts. This transplacental passage occurs despite injection of only small doses of a very highly protein bound drug into the subarachnoid space.

Key Words: ANESTHESIA—obstetric. ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES—spinal.

Nationally, spinal anesthesia is the preferred regional anesthetic technique for cesarean section (1,2). Because small quantities of local anesthetics are used for spinal anesthesia and the rates of drug absorption from the subarachnoid space are slow, it has been assumed that maternal blood levels are low or nondetectable (2). Furthermore, low maternal levels would mean that little of the local anesthetic agent would cross the placenta and reach the fetus (2).

These concepts were not tested until 1980 when Datta et al. reported detectable levels of lidocaine in both maternal and fetal plasma at delivery following subarachnoid injection (3). In 1986, Kuhnert et al. verified this finding and showed that individual parturients could have plasma lidocaine levels after subarachnoid injection that were within the range of those found after epidural injection (4). The latter study also showed that neonates excreted lidocaine and its metabolites in urine for more than 36 hr. Spinal anesthesia with lidocaine thus results in neonatal exposure to lidocaine.

The purpose of the present study was to measure the disposition of bupivacaine (which is more highly protein bound than lidocaine) and its metabolite in maternal, fetal, and neonatal plasma and neonatal urine after spinal anesthesia for elective cesarean section, and to compare these data with those previously obtained from this laboratory after bupivacaine epidural anesthesia (5).

Methods and Materials

Subject Population and Administration of Anesthesia

Six pregnant women and their infants were studied after delivery by elective repeat cesarean section at term. The patients were all ASA class I or II. The clinical characteristics of the mothers and neonates, the amounts of bupivacaine used, and the timing of anesthesia are shown in Tables 1 and 2. This study

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Table 1. Characteristics of the Maternal Study Population (n = 6)

Maternal characteristics	$\bar{X}$ ± SD	Range
Age (yr)	26 ± 5	18–31
Parity		
Nulliparous	0	—
Multiparous	6	—
Delivery method		
Elective repeat cesarean	6	—
Intrapartum anesthesia		
Total mg: 0.5% bupivacaine in 8% glucose	8.0 ± 0.5	7.5–8.5
Anesthesia—delivery interval (min)	31 ± 8	20–43
Complications		
Gestational diabetes	1	—
>200 lb	2	—

was approved by the Human Investigation Committee of Cleveland Metropolitan General Hospital and informed consent was obtained from each patient before inclusion in the study.

Each patient was hydrated with 1500 ml Ringer's lactate solution over 20 min prior to surgery. Sodium citrate (30 ml orally 10 min preoperatively) or cimetidine (300 mg intramuscularly 1–2 hr preoperatively) was given to each patient for aspiration pneumonitis prophylaxis. Patients were placed in a sitting position and lidocaine (2 ml of 1%) was injected subcutaneously at the L3–L4 interspace in the midline. A 25-gauge spinal needle with a 19-gauge introducer was used for dural puncture and aspiration of clear cerebrospinal fluid (CSF). Bupivacaine (7.5–8.5 mg or 1.5–1.7 ml 0.5% in 8% glucose) was injected into the subarachnoid space over 30 sec with aspiration of CSF at the start and conclusion of injection. The dose of bupivacaine was based on patient height and followed the recommendations of Santos et al. (6). Patients were then immediately placed supine with left lateral displacement of the uterus and a 10-degree Trendelenburg tilt (6). Adequate surgical anesthesia was obtained with sensory levels at T4–6 within 5–15 min. Supplemental oxygen was given by face mask from the time of abdominal incision until delivery of the neonate. All infants were delivered within 20–43 min after induction of spinal anesthesia. None of the infants had 1- or 5-min Apgar scores of less than 7 or a cord vein pH of less than 7.25 at delivery.

Sample Collection

Maternal peripheral venous blood samples (3 ml) were collected from an indwelling cannula in the arm opposite to that with intravenous infusion before and 1, 3, 5, 7, 10, 15, and 20 min after subarachnoid injection or until delivery and then every 30 min until 2–3 hr had elapsed since injection. A maternal venous sample was also obtained coincidently with clamping of the infant's cord. All samples were drawn into heparinized tubes and immediately placed on ice. The plasma was removed following centrifugation and frozen until assayed by gas chromatography/mass spectrometry (GC-MS). Neonatal blood samples obtained at birth from a doubly clamped section of umbilical cord and again 24 and 48 hr after delivery by either heel stick or venipuncture were obtained and handled in the same manner as maternal blood samples.

Table 2. Characteristics of the Neonatal Study Population

Neonatal characteristics	$\bar{X}$ ± SD	Range
Number of infants	6	—
Gestational age (weeks)	39.7 ± 1.0	38–41
Birth weight	3193 ± 211	2990–3600
Apgar score <7		
1 min	0	—
5 min	0	—
Cord venous pH	7.35 ± 0.06	7.25–7.41
Cord arterial pH	7.26 ± 0.05	7.19–7.29

Six consecutive 6-hr samples of neonatal urine were collected after delivery in plastic urine collection bags (Hollister Newborn U-bag). Neonatal urine collections were stopped if signs of skin irritation occurred. All urine samples were frozen until analyzed by GC-MS.

Sample Analysis

Levels of bupivacaine and its inactive metabolite, 2,6-pipecolylxylidine (PPX), which is produced by dealkylation, were determined in plasma and urine using a previously published GC-MS technique (5).

Semilogarithmic plots of levels of bupivacaine and PPX in maternal plasma were obtained by plotting concentrations of drugs in maternal plasma against minutes after the injection of bupivacaine. Fetal/maternal plasma concentration ratios and the ratio between cord arterial and cord venous bupivacaine concentration were obtained. Linear plots showing urinary levels of bupivacaine and PPX as a function of time were also constructed. Urinary levels of drug or metabolite data were expressed as ng/ml urine.

Statistical Analysis

Student's t-tests were used to compare levels of bupivacaine in maternal venous, cord venous, and cord

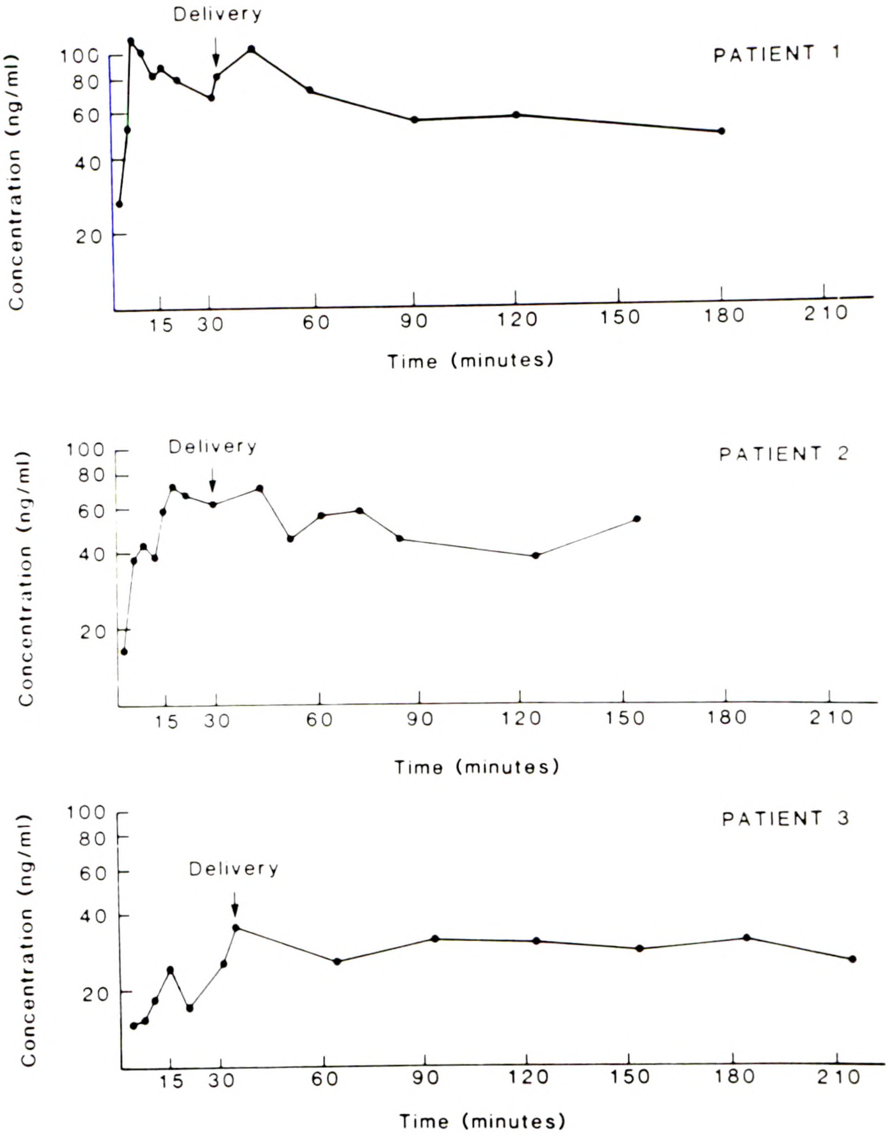

Figure 1. Plasma bupivacaine levels after spinal anesthesia for cesarean section.

arterial plasma after spinal or epidural anesthesia. Statistical significance was accepted at $P < 0.05$.

Results

Bupivacaine and PPX Levels in Maternal Plasma

Figure 1 shows plasma concentration–time profiles from three representative patients. These illustrate the similarity in the shape of the curves and also the range of bupivacaine levels seen. Concentration–time profiles for the other three patients were similar. PPX was not detectable prior to delivery. Bupivacaine was detectable in maternal plasma immediately after injection and usually fluctuated considerably prior to delivery. Mean peak maternal venous levels were 75.5 ± 32 ng/ml (range 36–113). Peak levels were reached at variable times following administration. In four of the patients, the peak levels were achieved in from 7 to 43 min; in the other two, peaks occurred at 144 and 110 min. The average time to the peak concentration was 59 ± 55 min in all six patients.

Mean levels of bupivacaine in maternal plasma at delivery are shown in Table 3 along with the ranges of values.

Fetal and Neonatal Plasma Levels

At delivery, all cord venous and arterial samples had detectable bupivacaine concentrations. Mean levels and range of values are shown in Table 3. The cord vein/maternal vein ratio ranged from 0.23 to 0.52. Cord artery/cord vein ratios as high as 1.22 were found. At

Table 3. Bupivacaine Concentrations in Maternal and Fetal Plasma at Delivery (ng/ml)

	Bupivacaine $\bar{X}$ ± SD	Bupivacaine Range
Maternal venous plasma[a]	59 ± 32	27–113
Fetal plasma		
Cord vein[b]	20 ± 7	11–29
Cord artery[c]	14 ± 5	10–20
Cord vein/maternal vein[b]	0.34 ± 0.12	0.23–0.52
Cord artery/cord vein[c]	0.81 ± 0.30	0.53–1.22

[a] n = 6.
[b] n = 5.
[c] n = 4.

24 hr after delivery, none of the neonates had detectable levels of bupivacaine in the 0.2–0.5-ml plasma samples that were obtained.

Neonatal Urine Levels

Eighteen urine samples were collected from six infants. No complete 36-hr collections were obtained. Because so few 6-hr samples were obtained, the data were combined to represent 12-hr collections. Data from the urine samples that were obtained indicate that bupivacaine and PPX are detectable in neonatal urine for at least 36 hr after spinal anesthesia (Fig. 2). The amount of bupivacaine excreted in urine decreased rapidly for 36 hr after delivery; the levels of PPX increased during the second 12 hr and then decreased more slowly than the bupivacaine. Levels of both compounds 36 hr after delivery suggested that excretion would continue for at least 72 hr.

Discussion

The purpose of this study was to describe the disposition of bupivacaine in mother, fetus, and neonate after bupivacaine spinal anesthesia for cesarean section. The key finding is that bupivacaine crosses the placenta and reaches the fetus, but in very low amounts. This transplacental passage occurs despite injection of only small doses of a very highly protein bound drug into the subarachnoid space.

The only other studies of bupivacaine levels after spinal anesthesia with which to compare this study reported values in nonpregnant patients (7,8). Burm et al. used gas chromatography (7) to measure plasma drug levels after subarachnoid injection of 15 mg hyperbaric bupivacaine in healthy nonpregnant females and males (age 18–50 yr) undergoing general surgical procedures on the lower limbs. Despite the fact that the dose of drug was twice that used in the present study, plasma levels of bupivacaine were similar. Burm et al. reported mean peak levels of 63 ± 22 ng and we report 76 ± 32 ng. Burm et al. also reported that the maximum concentrations occurred at a mean of 54 ± 11 min whereas in our study maximum plasma concentrations occurred at 59 ± 55 min. However, there was considerably more individual variation in the time of peak concentration in the pregnant patients. Furthermore, the shape of the parturient's concentration–time curves is more variable in the early absorption periods.

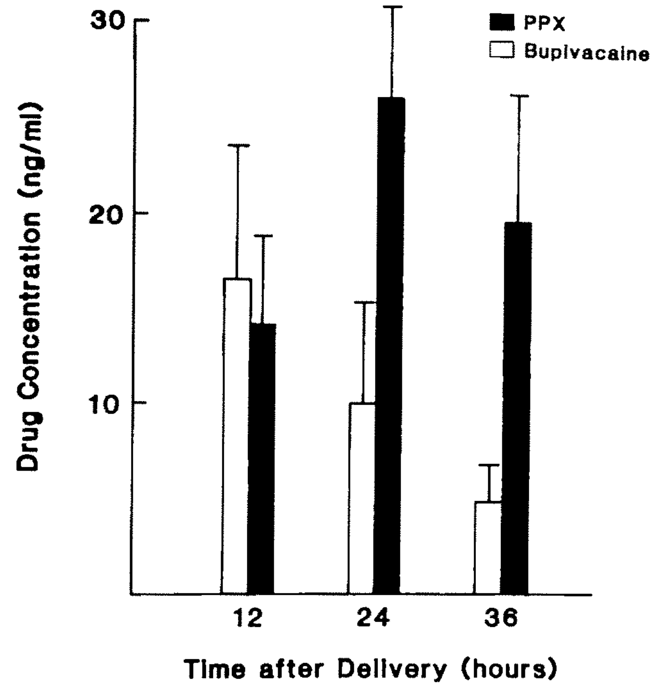

Figure 2. Neonatal excretion of bupivacaine and PPX for 36 hr after spinal anesthesia for delivery (x ± SEM).

In a second study, Axelsson et al. (8) used mass spectrometry to report bupivacaine levels in whole blood rather than plasma. They measured levels after subarachnoid injection of either 20 or 22.5 mg hyperbaric bupivacaine in patients (aged 58–89 yr) undergoing urological surgery. Their study is not directly comparable to our present study because of the use of whole blood, the higher doses of bupivacaine injected, and the older age of their patients. Their peak concentrations occurred at 98 ± 54 and 119 ± 72 min, respectively, with 20 and 22 mg of bupivacaine. Although the means are much higher, the individual variability was similar to what we report in pregnant patients.

Differences between the present study and other studies may also be attributable to differences in analytical techniques used to measure bupivacaine or to the fact that our patients were pregnant. Vascular absorption of local anesthetics injected into the subarachnoid space is thought to occur from the subarachnoid space, the epidural space, and the spinal cord itself (9). During pregnancy, increased intra-abdominal pressure causes venous engorgement, particularly in the epidural space (2). This results in decreased epidural space volume and possibly decreased volume of cerebral spinal fluid in the subarachnoid space. These changes could account for the increased variability in time of maximum concentration, the fluctuations noted in absorption of the drug, and the increased plasma levels despite the smaller dose of drug. Similar differences were noted in a comparison of the uptake of lidocaine from the subarachnoid space in pregnant and nonpregnant subjects (4).

After obstetrical bupivacaine epidural anesthesia, it is known that bupivacaine and PPX reach the infant and that bupivacaine appears in maternal plasma immediately after injection (5). The primary metabolite of bupivacaine, PPX, appears within 5 min. Fetal/maternal venous concentration ratios are 0.31 ± 0.06 and the cord arterial/cord venous ratios are 0.49 ± 0.34. Postpartum, both bupivacaine and PPX are detectable in neonatal plasma for 72 hr (5,10) and the infant excretes both compounds for at least 72 hr (5). The present study provides comparable data for disposition of bupivacaine after spinal anesthesia.

In the present study, mean maternal bupivacaine levels were 5% of those found after the higher doses of bupivacaine used for epidural anesthesia (5). Figure 3 compares the dosages, time from drug administration until delivery (DDI), and plasma levels of bupivacaine found after spinal anesthesia in the present study with those reported previously after epidural anesthesia (5). The differences in plasma levels are statistically significant. Mean cord venous plasma levels of bupivacaine after spinal anesthesia are 7% of those found after epidural anesthesia for cesarean section. Cord arterial plasma levels are also much lower (5). These differences (Fig. 3) are also statistically significant. Mean fetal/maternal ratios (0.34 ± 0.12) in the present study were not different from those found after epidural anesthesia (0.31 ± 0.06). Furthermore, mean cord artery/cord venous ratios (0.81 ± 0.31) in the present study were not significantly different from those found after epidural anesthesia (0.49 ± 0.43). The neonatal excretion patterns of bupivacaine and PPX were similar to those reported previously after epidural anesthesia (5).

It has been the general impression that concentrations of local anesthetics in maternal plasma never reach a level after spinal anesthesia that might possibly affect the fetus (2). In general, individual and mean maternal plasma levels are much lower than those reported previously after epidural anesthesia (5) and blood levels are achieved more slowly after spinal anesthesia. However, placental passage of the drug occurs and bupivacaine is taken up by fetal tissues. This is apparent from the neonatal excretion of the drug for at least 36 hr. Thus, bupivacaine crosses the placenta and reaches the fetus, but in very low amounts. This transplacental passage occurs despite injection of only small doses of a very highly protein bound drug into the subarachnoid space.

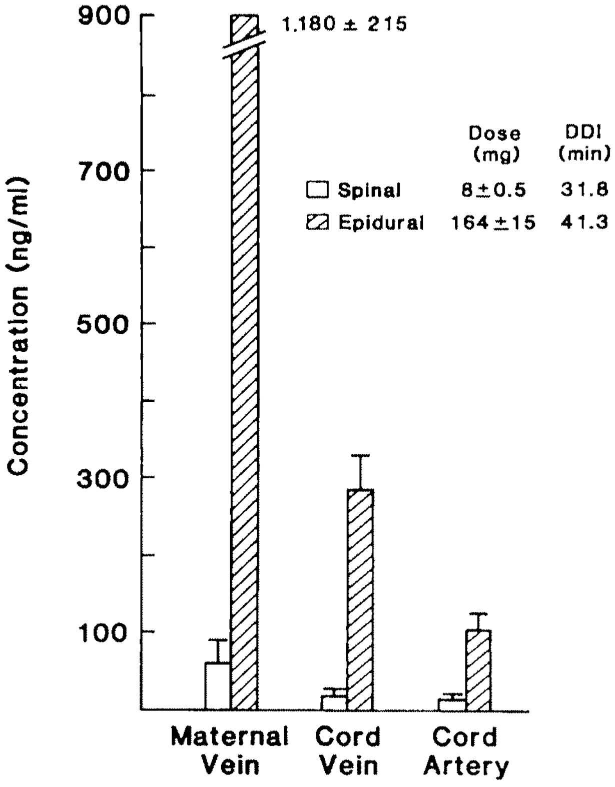

Figure 3. Comparison of plasma bupivacaine levels at delivery after spinal or epidural anesthesia (Kuhnert et al., Anesthesiology 55;611: 1981).

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Low-Dose Synthetic Narcotic Infusions for Cerebral Relaxation during Craniotomies

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BRISTOW A, SHALEV D, RICE B, LIPTON JM, GIESECKE AH Jr. Low dose synthetic narcotic infusions for cerebral relaxation during craniotomies. Anesth Analg 1987;66:413–6.

Thirty patients undergoing craniotomies were given infusions of fentanyl 1 μg·kg⁻¹·hr⁻¹, sufentanil 0.1 μg·kg⁻¹·hr⁻¹, or normal saline in a double-blind study of cerebral relaxation. Significantly better relaxation scores were achieved in patients given a narcotic infusion, but there was no difference between the scores with the two narcotics. Infusions of narcotics at these low rates did not delay recovery or alter the requirement for other anesthetic agents. Narcotic infusion rates that do not delay recovery or alter depth of anesthesia significantly improve cerebral relaxation.

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl, sufentanil. ANALGESICS—fentanyl, sufentanil. ANESTHESIA—neurosurgical.

Large doses of narcotics are often used in anesthesia for craniotomies because they decrease both cerebral blood flow and cerebral metabolic requirements. However, such doses often require the postoperative administration of naloxone, and it has been shown that naloxone significantly increases cerebral blood flow and cerebral oxygen requirements (1). This study was designed to determine whether smaller doses of narcotics, given by infusion, promote brain relaxation (2) and rapid postoperative recovery without requiring narcotic reversal postoperatively. Large doses of sufentanil have been shown to cause greater cardiovascular stability and more reliable brain relaxation than large doses of fentanyl (2). The effects of these two synthetic narcotics were therefore compared.

Methods and Materials

After the protocol was approved by the Institutional Review Board of our hospital, 30 patients who were to undergo elective craniotomies for either tumor, arteriovenous malformation, or aneurysm of cerebral vessels were selected for the study (mean ± SD age, yr: fentanyl group, 45 ± 15.1; sufentanil, 43.6 ± 13.1; saline 35.1 ± 11). Patients who had received intermittent positive pressure ventilation preoperatively or who had a history of cardiovascular disease other than angina were excluded, as were patients with an abnormal level of consciousness prior to anesthesia or with neurological symptoms other than localized motor weakness.

After informed consent was given, all patients received diazepam 10 mg and milk of magnesia 30 ml orally 2 hr before surgery. An 18-gauge intravenous cannula was inserted and, on arrival in the operating room, the radial artery and internal jugular vein were cannulated under local anesthesia.

All patients were randomly allocated to one of three groups. The fentanyl group received a bolus of 3 μg/kg prior to induction and an infusion of 1 μg·kg⁻¹·hr⁻¹. Patients given sufentanil received a bolus dose of 0.3 μg/kg and an infusion of 0.1 μg·kg⁻¹·hr⁻¹. The control group received a preinduction dose of 3 μg/kg fentanyl followed by an infusion of normal saline. The narcotic and saline infusions were prepared by one of the authors and assigned to patients according to a randomly generated list. All anesthetic procedures were carried out and records made by two of the other authors who were not aware of which drugs the patient received. One surgeon assessed cerebral relaxation and he was unaware of the contents of the infusion.

After induction of anesthesia with thiopental 3–5 μg/kg and administration of vecuronium bromide 0.1 μg/kg, the patient was intubated and stable anesthesia achieved with nitrous oxide and isoflurane. The latter was administered in concentrations to 1 MAC

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Table 1. Brain Relaxation Scores in Patients Undergoing Craniotomy

Score	Fentanyl	Sufentanil	Control
1	13	11	8
2	15	15	11
3–5	2	4	11

Table 2. Proportion of Cases Requiring Furosemide for Adequate Cerebral Relaxation

Fentanyl	Sufentanil	Saline
3/10	4/10	8/10

so as to prevent sweating, tachycardia, or hypertension in response to surgical stimulation, or other evidence of inadequate depth of anesthesia. The concentration was continually recorded against time by means of mass spectrometry. Isolated tachycardia after increased administration of isoflurane, that did not accompany surgical stimulus or hypertension, was treated with intravenous propranolol. Patients were hyperventilated to maintain a $Pa\text{CO}_2$ of 28 mm Hg measured by arterial blood gas analysis performed at the start and end of intracranial surgery. Mannitol 1 μg/kg and dexamethasone 0.15 μg/kg were given intravenously. A Foley catheter was inserted to monitor urine production.

The surgeon was asked to evaluate cerebral relaxation on a five-point scale from excellent (1) to poor (5). The score was based on five factors: tenseness of the brain tissue and ease of retraction, bulging of cerebral tissue from the edges of the craniotomy incision, flatness of sulci, dilatation of blood vessels, and the resultant ease of operation. All five factors had to be judged ideal for a score of 1. A score of 2 was awarded if retraction was not ideal and blood vessels were not fully constricted. A score of 3 indicated tense brain tissue that significantly hindered the procedure, combined with flat sulci and dilated blood vessels. A score of 4 represented a further deterioration in these factors with significant bulging of brain tissue from the skull, and 5 represented the worst possible conditions for surgery. Cerebral relaxation was assessed when the brain was first exposed, 90 min later, and immediately prior to closing the craniotomy.

Heart rate and systolic and diastolic blood pressures were measured via the arterial catheter. Central venous pressure was monitored via the jugular catheter. Measurements of these four functions were made prior to induction, after induction (lowest values and highest values), 5 min after surgical incision, and postoperatively. Hypotension, if indicated for the operation, was achieved with sodium nitroprusside. This was administered when the lesion (e.g., aneurysm) was visualized, and discontinued prior to closure. Hypotension was completely reversed prior to the end of the operation. Patients who were determined by the assessing surgeon to have brain tissue too tense to perform the procedure were given furosemide 40 mg IV. Additionally, one patient in the fentanyl group was given furosemide 40 mg IV for poor urine output following the third scoring. The fentanyl infusion was continued. The times from the end of the operation (placement of dressing) to maintenance of spontaneous respiration, extubation, and response to verbal commands were recorded. The total volumes of crystalloid solutions administered were recorded, as were the length of the procedure and the time from discontinuation of the isoflurane to the end of the operation. The amount of isoflurane used was recorded by plotting concentration against time on the mass spectrometer.

The narcotic infusion was discontinued when closure of the dura began. Normocapnia was achieved during the closure of skin and application of dressings. Neuromuscular relaxation was reversed with neostigmine 0.08 mg/kg and glycopyrolate 0.015 mg/kg, both given intravenously, as the dressing was being applied.

Two-way analysis of variance was used with one feature repeated to test for statistical significance of time effects, group effects, and time–group effects among the cardiovascular measures. One-way analysis of variance was performed to test the significance of differences in recovery times and in the amount of concomitant drugs administered. Also, χ^2 tests were used to test differences in the brain relaxation scores and in the requirement for additional therapy for brain relaxation among the groups.

Results

There were no differences among the three groups with respect to age, diagnosis, operation performed, ASA rating, or frequency and duration of use of sodium nitroprusside. The duration of anesthesia and surgery was similar in three groups. Table 1 gives the distribution of the three relaxation scores for the 30 patients (a total of 90 scores). Scores 3 to 5 have been placed in a single category because of the low incidence of these scores in the two groups receiving narcotics. There was no significant tendency, with respect to time, for relaxation scores either to improve or to deteriorate as the procedure progressed. Brain relaxation scores were significantly better in patients who received a narcotic infusion than in patients who

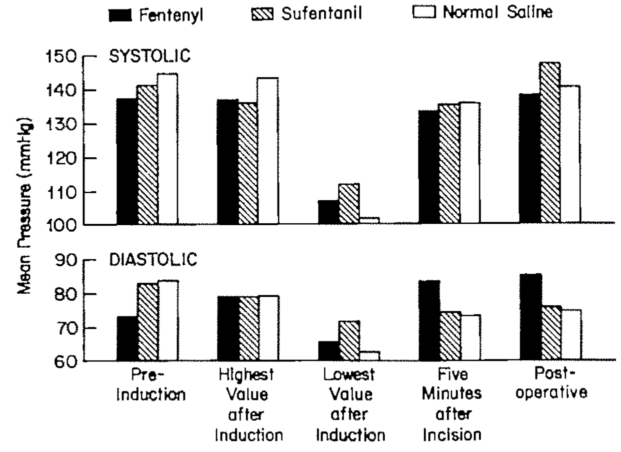

Figure 1. Mean systolic and diastolic blood pressures during anesthesia for craniotomy.

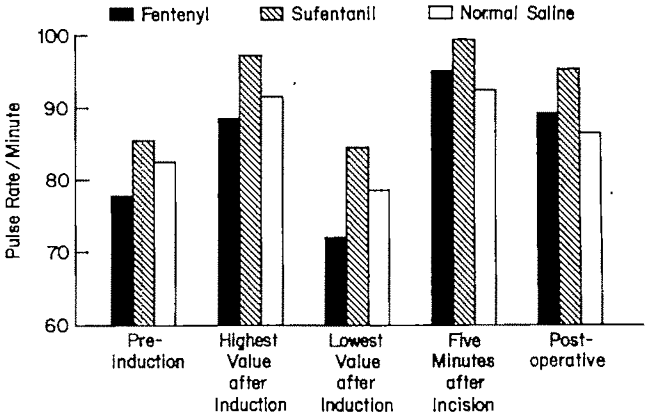

Figure 2. Mean pulse rates during anesthesia for craniotomy.

received saline preoperatively ($P < 0.05$). There was no difference between sufentanil and fentanyl with respect to brain relaxation ($P > 0.05$). The control group required additional therapy for brain relaxation more often than the two narcotic groups ($P < 0.05$, Table 2). Changes in cardiovascular variables over time were not different among the three groups (Figs. 1 and 2). None of the patients required naloxone. There were no differences among the three groups in dosages of thiopental, isoflurane, and propranolol; volumes of crystalloid solutions; incidence of intraoperative hypertension; incidence of induced hypotension; or recovery times (Tables 3 and 4).

Discussion

Cerebral relaxation reflects the degree of cerebral edema, the state of the cerebrovasculature, and the tension of the brain substance. Anesthetic techniques have been devised to optimize cerebral relaxation (3), an important component of satisfactory operating conditions. In the present study, no decrease in concomitant anesthetic agents was reported when low dose narcotic infusions were given, and recovery was not prolonged. Low dose narcotic infusions did, however, have a salutary effect on cerebral relaxation. The use of fentanyl or sufentanil for cerebral relaxation in doses too low to exert an anesthetic effect has two advantages over the use of large doses.

First, large dose narcotic administration frequently requires reversal by naloxone postoperatively to initiate and maintain spontaneous respiration. Naloxone can have adverse effects in neurosurgical patients because it increases cerebral blood flow and cerebral metabolic rate (1). Moreover, naloxone increases the incidence of nausea and vomiting to 23% (3) to 50% (4), which may severely increase intracranial pressure. Naloxone has also been reported to cause pulmonary edema (5), cardiac arrythmias (6), hypertension (7), rupture of intracranial aneurysms (8), and sudden death (9). None of the patients receiving low doses of narcotic required naloxone in this study. Second, high dose narcotics can cause epileptiform activity and seizures (1,10), to which neurosurgical patients are predisposed.

Table 3. Concomitant Medication (Mean ± SD[a])

	Fentanyl	Sufentanil	Saline
Thiopental (mg)	205 ± 47	190 ± 38	210 ± 41
Isoflurane (%)[a]	0.65 ± 0.15	0.78 ± 0.19	0.71 ± 0.16
Crystalloid solutions (ml)	2115 ± 1260	2910 ± 2083	3333 ± 1329
Propranolol (mg)	2.50 ± 2.27	2.60 ± 1.89	1.60 ± 1.71

[a] Averaged over the duration of anesthesia.

There was no difference in cerebral relaxation scores in this study related to whether fentanyl or sufentanil was given. This finding differs from that of previous studies in which high doses of sufentanil were found to be superior in achieving good cerebral relaxation (2). In this previous study, the ratio of fentanyl to sufentanil dose required for relaxation was between three to one and seven to one, although sufentanil is generally believed to be ten times as potent as fentanyl (11).

Although it would have been interesting to compare narcotic infusions with a control group given no narcotic, it was felt necessary to give our control group an initial single injection of fentanyl to reduce the stress of tracheal intubation. There was no difference

Table 4. Duration of Anesthesia and Time to Recovery (Min, Mean ± SD)

	Fentanyl	Sufentanil	Saline
Duration of anesthesia	391 ± 105	488 ± 277	437 ± 198
Interval from discontinuation of isoflurane to reversal of muscle relaxant	17.2 ± 6.2	27.6 ± 15.2	20.0 ± 7.8
Interval from reversal of muscle relaxant to spontaneous respiration	2.20 ± 3.72	1.07 ± 1.52	1.20 ± 1.55
Interval from reversal of muscle relaxant to extubation	7.30 ± 4.80	13.30 ± 6.91	9.40 ± 5.10
Interval from reversal of muscle relaxant to verbalization	10.20 ± 8.24	16.45 ± 10.48	17.05 ± 13.86

in the peak cardiovascular responses to induction and intubation in the three groups. This allows a comparison of the initial relaxation scores to be made, since induction and intubation had the same effect in all three groups. The absence of a significant change, or trend, in relaxation scores as the cases progressed suggests that narcotic infusions achieve their effect prior to exposure of the brain.

Our patients were able to verbalize within less than 14 min after reversal of neuromuscular blockade. This rapid recovery allows early postoperative neurologic assessment of the patient. Recovery times were fairly consistent and were shorter than those reported by others after large doses of narcotics (3,4).

Low dose narcotic infusions obviate the requirement for naxolone and the long recovery times observed with large doses of narcotics, and at the same time provide better cerebral relaxation and decrease the need for extra medication than is possible with totally inhalational anesthetic techniques. Thus, low dose narcotic techniques more closely approach the ideal anesthetic agent for neurosurgery described by Michenfelder et al. (12). The cerebral relaxation score used in the present study also confirmed the experience of others (2) that it is possible to quantitate the intracranial operative conditions and thus evaluate and compare the merits of various anesthetic techniques in intracranial operations.

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Local Analgesia without Anesthesia Using Peripheral Perineural Morphine Injections

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MAYS KS, LIPMAN JJ, SCHNAPP M. Local analgesia without anesthesia using peripheral perineural morphine injection. Anesth Analg 1987;66:417–20.

Twenty-five patients with chronic pain were treated with nerve blocks. They were divided into two groups, A and B, according to the volume of local anesthetic required for surgical anesthesia by standard nerve block techniques. The 16 patients in group A had pain in the distribution of small nerves, which could be blocked with 5 ml or less. They were blocked in a random, double-blind crossover fashion using 0.5% bupivacaine or 0.02% morphine. The nine patients in group B were injected simultaneously with saline, 30 ml perineurally and 1 ml intramuscularly. Morphine (6 mg) was added, in a random, double-blind fashion, to one of the injections. A second pair of injections was subsequently done, using morphine by the alternative route. Perineural morphine provided statistically longer lasting pain relief than did either intramuscular morphine or perineural bupivacaine.

Key Words: PAIN—chronic. ANALGESICS—morphine. ANESTHETICS, LOCAL—bupivacaine.

Studies of the mechanisms of action of opiates have revealed that specific receptors exist for these compounds (1) and for their endogenous ligands, the endorphins (2). This has led to the development of new methods of pain control, including intrathecal (3), epidural (4), and intracerebroventricular (5) injections of opiates. Additionally, the findings that opiate binding areas occur within the peripheral sympathetic ganglia led to the findings by Mays et al. (6,7) that opiate injections into these peripheral nerve sites relieve pain.

Reports as long ago as those by Rynd in 1845 (8) and Wood in 1855 (9) described prolonged relief from chronic intractable pain with peripheral somatic distribution, using peripheral perineural injections of opiates. Mitchell, in 1872 (10), spoke of the beneficial effects of opiates injected within the painful area (as opposed to administration by other systemic routes) in the treatment of patients with causalgia.

Based on the above findings, we tested, in an open study (11), the effects of perineural somatic injections of dilute solutions of morphine in patients with chronic pain, with good initial results. The present paper was designed to evaluate, in a controlled fashion, the clinical usefulness of these injections.

Methods

Twenty-five patients referred to the University of Tennessee Pain Clinic or the Pain Unit of the Baptist Memorial Hospital with chronic intractable pain amenable to nerve block therapy were entered into the study, which was approved by the Institutional Review Boards of both institutions. Informed consent was obtained in all cases after a full disclosure of the procedure to the patient. Patients whose pain could not be blocked with a single injection of conventional local anesthetic were excluded (for example, those suffering from herpes zoster involving more than one thoracic dermatome), as were patients receiving opioid medication. Patients were assigned into two treatment groups, A and B (Table 1).

Group A ($n = 16$) consisted of patients in whom pain was transmitted along nerves small enough that they could be blocked by 5 ml or less of local anesthetic solution. These patients received either 0.5% bupivacaine hydrochloride or 0.02% morphine sulfate in a preservative-free normal saline solution in similar volumes in a random, double-blind, crossover fashion using standard nerve block techniques. The 0.5% bupivacaine hydrochloride is a standard long-acting local anesthetic solution. The 0.02% morphine sulfate solution was chosen after reviewing the early literature. Pain relief was evaluated using a verbal response scale (VRS: 0 = no relief, 1 = a little relief, 2 = a lot of relief, 3 = almost complete relief, 4 = complete relief) at 15 min and at 4, 12, and 24 hr after injection.

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Table 1. Patient Groups and Morphine Doses

Nerve/plexus	Volume (ml)	Dose of morphine (mg)	Patients
Group A (n = 16)			
Supratrochlear nerve	0.2	0.04	1
Supraorbital nerve	1.0	0.2	2
Intercostal nerve	1.0	0.2	7
Occipital nerve	3.0	0.6	3
Median nerve	5.0	1.0	1
Radial nerve	5.0	1.0	1
L2 root	5.0	1.0	1
Group B (n = 9)			
Brachial plexus	30.0	6.0	6
Sciatic nerve	30.0	6.0	3

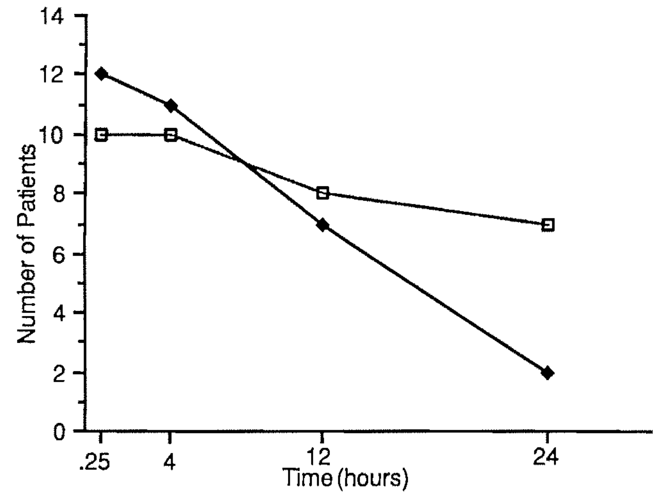

Figure 1. Number of patients in group A in whom pain relief on the verbal response scale was 2 or more (see "Methods") at various times after perineural injection of morphine (-⊟-) or bupivacaine (-◆-).

The second injection, either bupivacaine or morphine, was administered to each patient by the same route when pain approached preinjection levels after the first treatment (24 hr to 2 weeks).

Group B consisted of patients (n = 9) in whom pain transmission involved peripheral nerves or plexuses so large as to require 30 ml, not 5 ml or less, of anesthetic solution to be blocked (e.g., the sciatic nerve or the brachial plexus). In group B, each patient received either morphine sulfate, 6 mg/30 ml perineurally, and 1.0 ml of saline intramuscularly, or, at a different time, morphine sulfate, 6.0 mg/1.0 ml intramuscularly, and 30 ml of saline perineurally. Both sets of injections were performed in a double-blind, crossover fashion. The second set was made after the pain approached pretreatment levels. For convenience, pain was evaluated in this group by means of the classic 10-cm visual analogue scale (VAS) instead of the VRS, at the same time intervals as for group A.

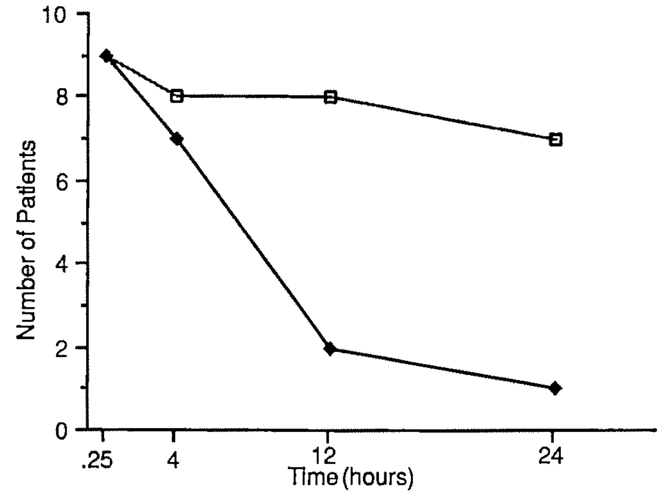

Figure 2. Number of patients in group B in whom pain on the visual analogue scale (see "Methods") was relieved by 50% or more following perineural (-⊟-) or intramuscular (-◆-) morphine.

All patients were examined before and after injection, at each time interval, for sensory, motor, and sympathetic function, as appropriate. Objective signs (urticaria, miosis) and subjective signs (euphoria, dysphoria) of systemic opiate effects were also evaluated.

Pain relief was considered significant when reduced by 50% or more on the VAS or rated as 2 or more on the VRS. The number of patients with significant pain relief after perineural morphine at each time interval was compared with the number of patients who obtained relief after either the local anesthetic or perineural saline injection. The data were analyzed using the χ^2 test, a probability of 0.05 or less being considered statistically significant.

Results

Group A

The difference in the number of the 16 patients studied who achieved early pain relief (VRS 2 or more) with either morphine or bupivacaine was not statistically significant (Fig. 1). However, at 24 hr, seven patients injected with perineural morphine still had pain relief whereas only two patients reported continued relief after bupivacaine ($P < 0.01$). No hypesthesia, weakness, or autonomic changes, regularly seen with bupivacaine, were observed after morphine injection. Neither treatment produced objective or subjective central effects.

Group B

All nine patients obtained initial pain relief with both perineural and intramuscular morphine (Fig. 2). The analgesia persisted in more patients in the perineurally injected group at 12 hr (eight of nine) and at 24 hr (seven of nine) than in those patients receiving morphine by intramuscular injection [two of nine and one of nine, respectively ($P < 0.05$)]. No patients had sensory, motor, or autonomic impairment after either treatment.

Discussion

The present results suggest that morphine injected around nerves acts differently than either local anesthetics or systemic morphine in providing relief for patients with chronic pain. A mechanism to account for the current findings must include an explanation of the fact that morphine produced local analgesia without local anesthesia and that its duration of action was longer than that of systemic morphine in one instance and of bupivacaine in the other.

Reports of morphine's action on peripheral nerves are somewhat contradictory with regard to the question of either receptor-mediated or nonspecific action. Jurna and Grossman (12) have demonstrated a selective effect of morphine in different types of nerve fibers, increasing the compound action potential of A-β fibers while reducing that of A-δ and C fibers; these effects were reversed by naloxone. Morphine also increased both the absolute and relative refractory periods, effects that were also reversed by naloxone, a characteristic of opiate receptor mediation.

Other investigators have found that morphine's effects on peripheral nerves are not reversed by naloxone. Schefner et al. (13) have shown that in the vagus nerve preparation, morphine (0.1 mM) depressed the action potential evoked on the vagal axon and recorded on the cell body. This effect was reversed by washing, but not by naloxone (0.5 mM). (For comparison, in our study we utilized a solution of 0.3 mM morphine.) However, in an elegant experiment, Yuge et al. (14) were not able to demonstrate any significant change in the compound action potential of either A-β, A-δ, or C fibers after perineural application of morphine. This strongly argues against a possible local anesthetic effect of morphine but leaves unanswered the eventual effect of morphine on a train of impulses traveling along the nerve, as a small increase in the refractory period of the axon could account for significant changes in its capacity to carry a high frequency of discharge.

In a different set of experiments, Smith et al. (15) demonstrated that n-methyl morphine (a morphine quaternary analogue that does not cross the blood–brain barrier) has a naloxone-reversible antinociceptive action in mice, again suggesting a peripheral analgesic action. It is possible that axonal uptake and transport of morphine to the spinal cord or to the peripheral tissues could account in part for the prolonged relief observed, as opiates have been shown to act as potent analgesics in both locations (16,17).

Other clinical reports on the analgesic effects of perineural morphine in humans have been published (18,19), and the findings again have been contradictory. Bullingham's failure to relieve acute postoperative pain (18) may be attributable to the differences in the nature of acute and chronic pain.

Although this study was limited to a 24-hr follow-up period, further observations of these and other patients demonstrated in most a much longer duration of relief with morphine perineurally than with bupivacaine. Our experience in the past 5 yr, with the use of morphine for perineural injections in patients with chronic pain leads us to believe that the procedure is clinically more effective than local anesthetic injections and has no significant morbidity.

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Endocrine and Hemodynamic Effects of Antagonism of Fentanyl-Induced Respiratory Depression by Nalbuphine

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ZSIGMOND EK, DURRANI Z, BARABAS E, WANG XY, TRAN L. Endocrine and hemodynamic effects of antagonism of fentanyl-induced respiratory depression by nalbuphine. Anesth Analg 1987;66:421–6.

Endocrine and hemodynamic changes associated with the antagonism of fentanyl by nalbuphine have not been reported. Therefore, the authors studied ten patients after anesthetic induction with thiopental, fentanyl, tracheal intubation aided by succinylcholine and maintenance with diazepam, pancuronium, N_2O, and further doses of fentanyl. Eight of the patients underwent cholecystectomy, one had a hysterectomy, and another had an abdominoplasty.

After reversal of neuromuscular block at the conclusion of surgery, normal ventilation was restored by 0.22 ± 0.02 mg/kg intravenous nalbuphine (mean ± SEM). Plasma levels of free norepinephrine, histamine, and cortisol did not increase after antagonism of the fentanyl-induced respiratory depression, but plasma concentration of epinephrine increased significantly but without significant hemodynamic changes. Minute ventilation was 1.5 ± 0.4 L/min before and 11 ± 1, 10 ± 1, 11 ± 1, and 10 ± 1 L/min at 15, 30, 45, and 60 min after antagonism; corresponding Pa_{CO_2} levels were 56 ± 2, 44 ± 1, 49 ± 7, 49 ± 1, 42 ± 1 mm Hg. The mean analogue pain score remained below 1.5. We conclude that nalbuphine effectively antagonizes fentanyl-induced respiratory depression without adverse endocrine and circulatory changes or loss of analgesia.

Key Words: ANALGESICS—fentanyl, nalbuphine. ANTAGONISTS—nalbuphine.

A well-recognized adverse effect of moderate to large doses of fentanyl as an analgesic component for neuroleptanalgesia is prolonged postoperative respiratory depression requiring mechanical ventilation and/or reversal by naloxone. The reversal of respiratory depression caused by fentanyl with IV naloxone occasionally causes simultaneous reversal of analgesia and adverse hemodynamic changes that may be related to reversal of analgesia (1–3). Julien (4), Latasch et al. (5), Moldenhauer et al. (6), and Tabatabai et al. (7) demonstrated that respiratory depression caused by analgesic agonists could be antagonized by intravenous administration of the agonist-antagonist nalbuphine without concomitant reversal of analgesia (5–7) or adverse hemodynamic changes in most cardiac patients (6). Endocrine changes (e.g., catecholamine and cortisol concentrations) associated with nalbuphine antagonism of respiratory depression, however, have not been thoroughly investigated as yet. We, therefore, undertook a study of catecholamine and cortisol concentrations associated with the antagonism of fentanyl-induced respiratory depression by nalbuphine, and also evaluated the effect of reversal on ventilation and analgesia. Since an antagonist without histamine-releasing potential may be safer than one with histamine-releasing properties, plasma histamine concentrations were also determined.

Materials and Methods

In an open study, ten patients scheduled for elective abdominal surgery (Table 1), all females and nonsmokers, with a mean age ± SEM of 36.0 ± 4.8 yr and a mean weight of 69.0 ± 3.7 kg, were studied. All patients were ASA physical status class I or II and gave written informed consent as required by our Institutional Research Review Board.

After 1.5 mg/kg hydroxyzine IM and 3.0 μg/kg glycopyrrolate IM as premedication, anesthesia was induced with 4.2 ± 0.5 mg/kg thiopental, followed by 0.41 ± 0.1 mg/kg diazepam, 11.0 ± 1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ fentanyl given in incremental doses, and $N_2O:O_2$, 3:2 L/min. Tracheal intubation was facilitated with 1.0 mg/kg succinylcholine. Pancuronium, 0.1 ± 0.01 mg/kg, was used for intraoperative maintenance of

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Table 1. Duration and Type of Surgery

Patient no.	Surgery type	Duration of surgery (min)
1	Cholecystectomy	135
2	Cholecystectomy	260
3	Hysterectomy	120
4	Abdominoplasty	290
5	Cholecystectomy	150
6	Cholecystectomy	150
7	Cholecystectomy	150
8	Cholecystectomy	165
9	Cholecystectomy	325
10	Cholecystectomy	295

muscle relaxation. Arterial $PaO_2 > 100$ mm Hg and $PaCO_2$ in the range of 28–38 mm Hg were maintained throughout anesthesia by adjusting mechanical ventilation based on the capnographic measurements and measurements of blood gas tensions using an ABL-4 Radiometer blood gas analyzer at least every hour as well as 30 min and 15 min before nalbuphine antagonism and every 15 min for an hour afterward. Ventilation was monitored by chest plethysmography (Gilson), spirometry (Wright), and capnography (Puritan-Bennett) on a multichannel recorder. Direct radial arterial pressure (AP) was determined via a Gould-Statham strain gauge, and ECG lead V_5 or lead with the tallest R-wave was monitored on a Gilson polygraph.

The monitoring equipment was carried with the patient to the recovery room. The muscle relaxant effect of pancuronium was continually monitored throughout anesthesia. Before the administration of pancuronium, the twitch height, train of four, and tetanic response of the adductor pollicis hand muscle to ulnar nerve stimulation were recorded. At the end of the surgical procedure, 0.25 mg/kg pyridostigmine and 4.0 μg/kg glycopyrrolate were given IV for reversal of neuromuscular blockade. After recovery of twitch height to 95% of the initial value, mechanical ventilation was discontinued and manual assistance of spontaneous ventilation begun. Alveolar CO_2 was allowed to increase to 56 mm Hg by reducing manual ventilation until patients regained spontaneous but inadequate ventilatory drive. Severe ventilatory depression and/or apnea lasting for 30 sec was sustained before 0.1 mg/kg nalbuphine was given IV. If adequate ventilation was not restored within 3 min, an additional 0.1 mg/kg nalbuphine was given IV every 3 min until full recovery to the level of minute ventilation maintained prior to termination of anesthesia by assisted ventilation was achieved, a level that assured a normal $PaCO_2$. Extubation was carried out within 15 min after nalbuphine administration. During transportation to and while in the recovery room, the patients breathed O_2-enriched air after the administration of nalbuphine.

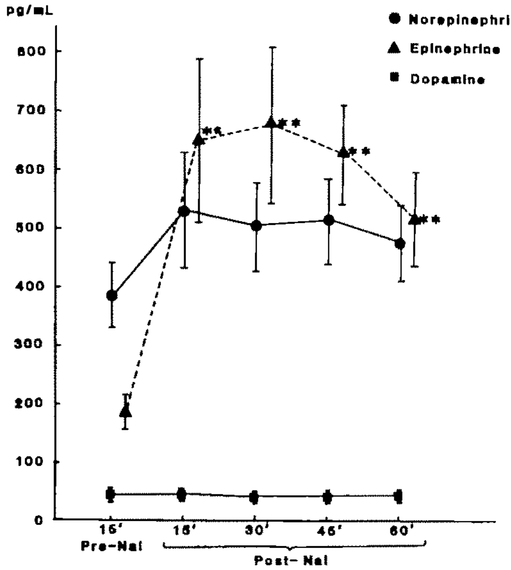

Figure 1. Plasma catecholamine levels after nalbuphine antagonism of fentanyl-induced respiratory depression. Epinephrine levels are significantly above baseline levels: ** = $P \leq 0.01$.

Plasma-free catecholamine levels of epinephrine, norepinephrine, and dopamine were determined 15 min before and 15, 30, 45, and 60 min after nalbuphine by a high-performance liquid chromatographic (HPLC) assay (8,9) in plasma samples stored at −30°C that were derived from blood samples taken into heparinized tubes kept at −4°C and centrifuged in a refrigerated centrifuge. Plasma-free cortisol concentrations were determined by a radioimmunoassay (10). Plasma histamine concentrations were measured by a spectrofluorometric assay (11). Duplicate determinations were carried out on each blood sample and on internal controls with these hormones. Diazepam, fentanyl, nalbuphine, thiopental, and pancuronium in the expected blood concentrations caused no interference with the catecholamine, cortisol, or histamine assays.

Pain scores were determined on a visual analogue pain scale 15, 30, 45, and 60 min after nalbuphine administration. Since the patients were still narcotized and intubated at the time of nalbuphine antagonism, the visual analogue pain scores could not be determined. A period of 15 min was necessary for evaluating ventilation and safely extubating the patients; hence this was the first opportunity to record pain scores. Preoperative instruction was given to the patients to assure understanding of the scale. On this scale, 10 is the most severe pain and 0 represents no pain. The time interval between nalbuphine administration and the first narcotic dose was recorded. Side effects were observed and recorded on a case report form.

All values are expressed as means ± SEM.

Statistical analyses were carried out by utilizing the one-sample t-test, which uses as the sample the differences between the value at the control time (-15 or 0 min) and each sample time. Determination of significance was also done by the two-sample t-test, but the one-sample t-test was superior because each patient at each time is paired with his or her own control.

Results

Endocrine Effects

No significant changes in mean plasma-free norepinephrine or dopamine concentrations were observed at any time after nalbuphine antagonism of the fentanyl-induced respiratory depression (Fig. 1). Mean plasma-free epinephrine concentrations increased significantly at 15, 30, 45, and 60 min ($P \leq 0.01$). Mean plasma cortisol levels did not increase after antagonism, nor did plasma histamine levels increase after nalbuphine (Fig. 2).

Hemodynamics

No significant increases in heart rate or systolic or diastolic pressure were observed following nalbuphine (Fig. 3). No arrhythmias occurred.

Ventilatory Effects

Apnea was antagonized by a mean nalbuphine dose of 0.22 ± 0.02 mg/kg and normal ventilation restored during the 60-min observation period in all ten patients. A single dose of nalbuphine was required by one patient; two doses of nalbuphine were required by seven patients; one patient required three doses; and one patient required four doses. Ventilatory changes after antagonism by nalbuphine were as shown in Table 2.

Respiratory rates and minute volumes were significantly ($P < 0.001$) lower at the time of nalbuphine administration (0 min) than they were 15 min before nalbuphine administration. Statistically significant ($P < 0.001$) increases in both respiratory rate and minute volume observed 15 min after nalbuphine injection were sustained throughout the 1-hr observation period (Table 2).

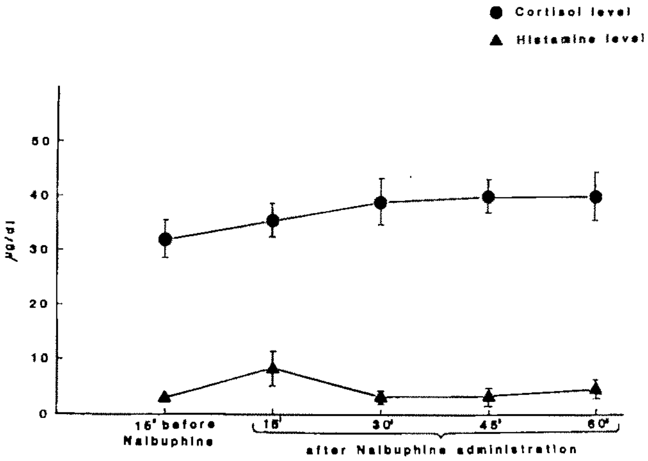

Figure 2. Changes in cortisol and histamine levels after nalbuphine antagonism of fentanyl-induced respiratory depression. None of the levels is significantly different from baseline.

Mean $PaCO_2$ before antagonism, 56.3 ± 1.6 mm Hg, decreased significantly after antagonism by nalbuphine (Table 2). Since patients breathed oxygen before and after administration of nalbuphine, PaO_2 values were elevated above baseline normal values before and after the antagonism. The large standard errors also indicate marked variations in inhaled oxygen concentrations. Mean arterial pH and base excess (BE) were not significantly altered throughout the 1-hr observation period after antagonism. No patient had recurrence of respiratory depression in the 24 hr after the 60-min observation period.

Pain Relief

Pain scores, utilizing an analogue scale of 0–10, did not increase until from 15–60 min after nalbuphine antagonism of the fentanyl-induced respiratory depression (Table 3). No earlier accurate determination of the analogue pain scores than at 15 min was possible, since the patients remained narcotized and intubated at the time of nalbuphine antagonism. The 15-min time period was necessary for recording ventilatory/circulatory changes and extubating the patients. The time before administration of the first postoperative analgesic medication given at the request of the patient averaged 636.6 ± 189.7 min after nalbuphine injection. Shivering and restlessness were observed in three patients after nalbuphine administration and extubation.

Discussion

Antagonism of respiratory depression by analgesic antagonists such as *n*-allyl-normorphine or levallorphan may be associated with adverse circulatory ef-

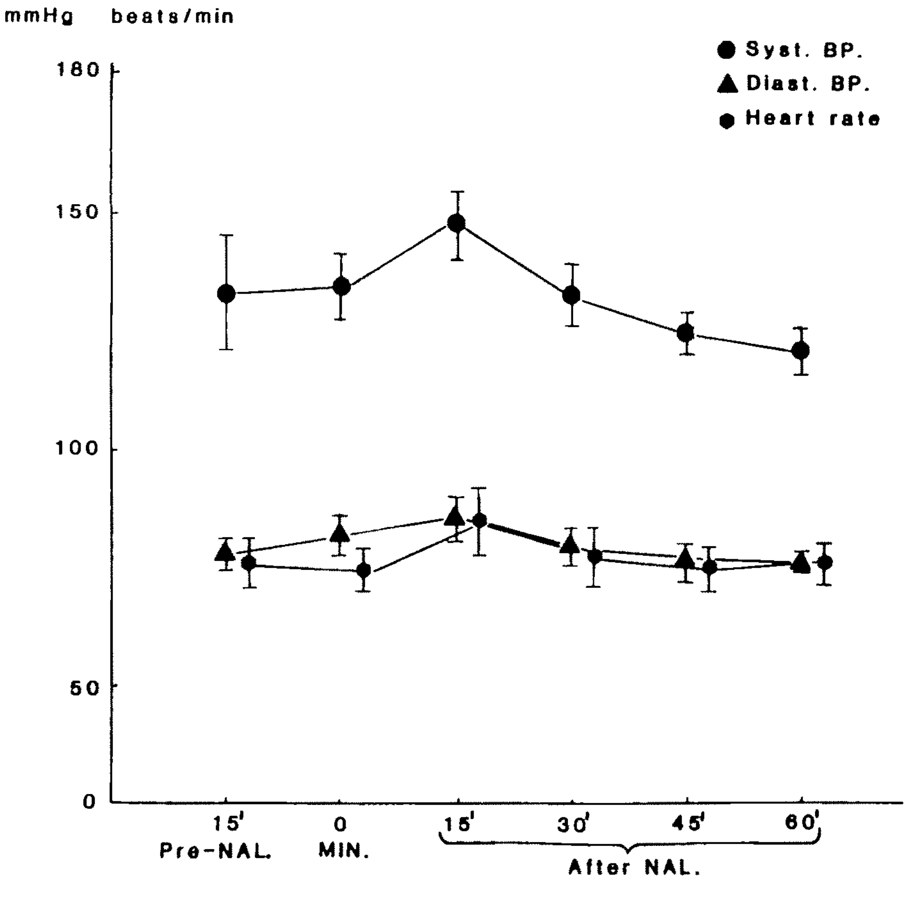

Figure 3. Circulatory changes after nalbuphine antagonism of fentanyl-induced respiratory depression. None of the changes is significantly different from baseline levels 15 min before nalbuphine was given.

fects. Naloxone, a more selective narcotic antagonist, has a better therapeutic index, but adverse circulatory effects have been reported after its use (1–3). Although it is still debated as to whether some of these circulatory effects are related to the recurrence of pain after reversal, some reports claim that naloxone per se causes these effects. Since we observed no adverse circulatory changes and no increase in norepinephrine and cortisol concentrations after antagonism of the respiratory depressant effect of fentanyl by nalbuphine, nalbuphine represents a viable alternative to naloxone for antagonism of respiratory depression induced by mu-agonist narcotics. The lack of histamine release after antagonism by nalbuphine may be particularly advantageous in patients with asthma or allergic diathesis.

Antagonism of the respiratory depressant effects of fentanyl was achieved at the end of anesthesia by intravenous nalbuphine administration in doses lower than those necessary for relief of postoperative pain (12–14). This observation is in accord with a number of recent reports (4–7). Whether nalbuphine in the doses utilized further added to the pain relief of fentanyl or provided pain relief per se cannot be answered from our study. One of the shortcomings of our experimental design was our inability to score pain in an accurate way prior to the administration of nalbuphine (0 min) in spite of the preoperative teaching of the patients. A few patients were able to indicate pain intensity on the analogue scale, however, the majority were narcotized and uncooperative at the time of nalbuphine administration. Thus, we were able to evaluate pain scores only from 15 to 60 min after the administration of nalbuphine. The fact that the mean analogue pain scores remained less than 1.5 units during this 45-min observation period certainly suggests, as do the catecholamine and cortisol blood levels, that pain was not being experienced—that is, that analgesia provided by the fentanyl was not being reversed. Furthermore, the long time between antagonism and administration of the first analgesic postoperatively certainly indicates the absence of pain in the immediate postoperative period following nalbuphine.

Moreover, the lack of increase in plasma norepinephrine is additional evidence that the patients experienced no pain during the observation period, since, as we previously reported, pain increases norepinephrine levels (15). In that earlier paper, we studied 80 patients who had recovered from enflurane anes-pain. The time interval between nalbuphine administration and the first narcotic dose was recorded. Side effects were observed and recorded on a case report form.

All values are expressed as means ± SEM.

Statistical analyses were carried out by utilizing the one-sample *t*-test, which uses as the sample the differences between the value at the control time (−15 or 0 min) and each sample time. Determination of significance was also done by the two-sample *t*-test, but the one-sample *t*-test was superior because each patient at each time is paired with his or her own control.

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Mean Pa_{CO_2} before antagonism, 56.3 ± 1.6 mm Hg, decreased significantly after antagonism by nalbuphine (Table 2). Since patients breathed oxygen before and after administration of nalbuphine, Pa_{O_2} values were elevated above baseline normal values before and after the antagonism. The large standard errors also indicate marked variations in inhaled oxygen concentrations. Mean arterial pH and base excess (BE) were not significantly altered throughout the 1-hr observation period after antagonism. No patient had recurrence of respiratory depression in the 24 hr after the 60-min observation period.

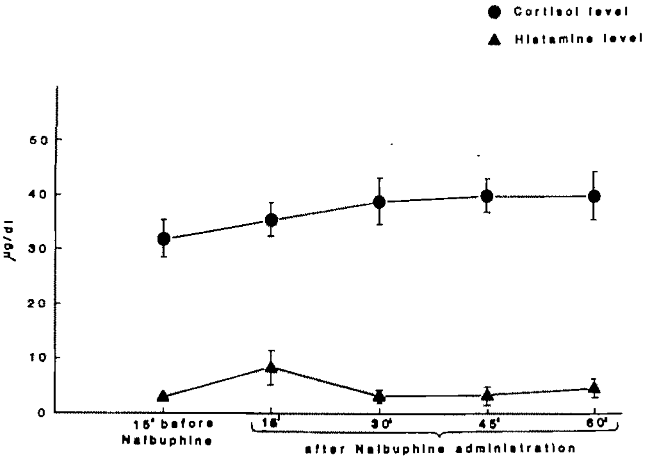

Figure 2. Changes in cortisol and histamine levels after nalbuphine antagonism of fentanyl-induced respiratory depression. None of the levels is significantly different from baseline.

Pain Relief

Pain scores, utilizing an analogue scale of 0–10, did not increase until from 15–60 min after nalbuphine antagonism of the fentanyl-induced respiratory depression (Table 3). No earlier accurate determination of the analogue pain scores than at 15 min was possible, since the patients remained narcotized and intubated at the time of nalbuphine antagonism. The 15-min time period was necessary for recording ventilatory/circulatory changes and extubating the patients. The time before administration of the first postoperative analgesic medication given at the request of the patient averaged 636.6 ± 189.7 min after nalbuphine injection. Shivering and restlessness were observed in three patients after nalbuphine administration and extubation.

Discussion

Antagonism of respiratory depression by analgesic antagonists such as *n*-allyl-normorphine or levallorphan may be associated with adverse circulatory ef-

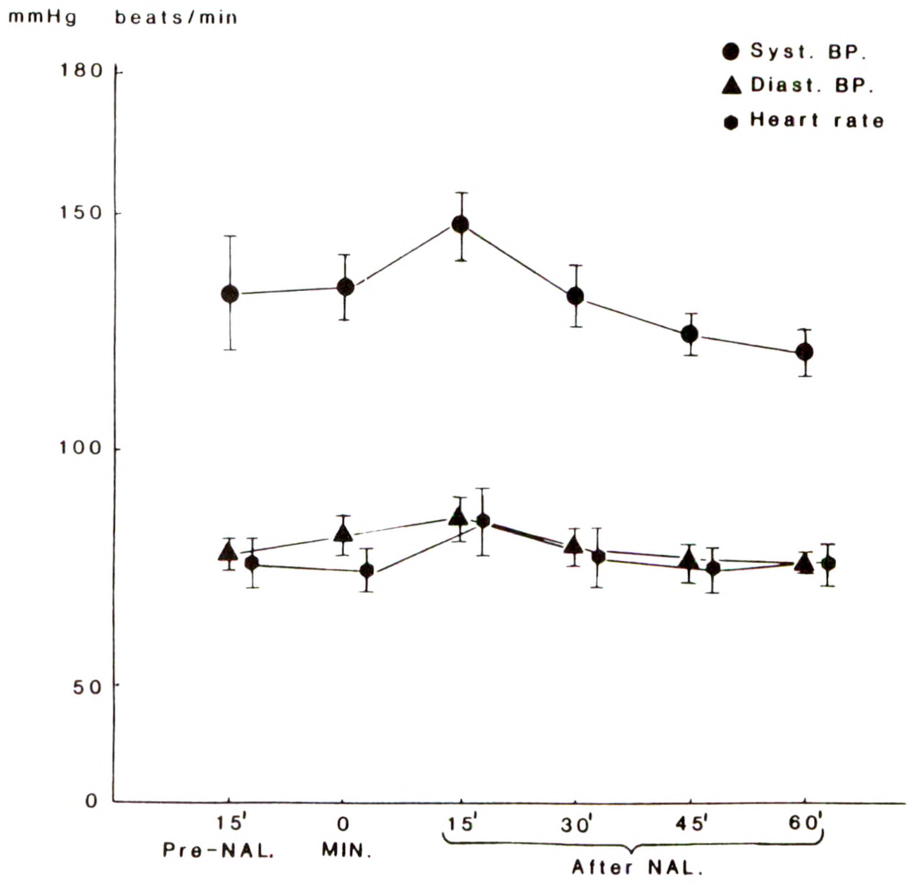

Figure 3. Circulatory changes after nalbuphine antagonism of fentanyl-induced respiratory depression. None of the changes is significantly different from baseline levels 15 min before nalbuphine was given.

fects. Naloxone, a more selective narcotic antagonist, has a better therapeutic index, but adverse circulatory effects have been reported after its use (1–3). Although it is still debated as to whether some of these circulatory effects are related to the recurrence of pain after reversal, some reports claim that naloxone per se causes these effects. Since we observed no adverse circulatory changes and no increase in norepinephrine and cortisol concentrations after antagonism of the respiratory depressant effect of fentanyl by nalbuphine, nalbuphine represents a viable alternative to naloxone for antagonism of respiratory depression induced by mu-agonist narcotics. The lack of histamine release after antagonism by nalbuphine may be particularly advantageous in patients with asthma or allergic diathesis.

Antagonism of the respiratory depressant effects of fentanyl was achieved at the end of anesthesia by intravenous nalbuphine administration in doses lower than those necessary for relief of postoperative pain (12–14). This observation is in accord with a number of recent reports (4–7). Whether nalbuphine in the doses utilized further added to the pain relief of fentanyl or provided pain relief per se cannot be answered from our study. One of the shortcomings of our experimental design was our inability to score pain in an accurate way prior to the administration of nalbuphine (0 min) in spite of the preoperative teaching of the patients. A few patients were able to indicate pain intensity on the analogue scale, however, the majority were narcotized and uncooperative at the time of nalbuphine administration. Thus, we were able to evaluate pain scores only from 15 to 60 min after the administration of nalbuphine. The fact that the mean analogue pain scores remained less than 1.5 units during this 45-min observation period certainly suggests, as do the catecholamine and cortisol blood levels, that pain was not being experienced—that is, that analgesia provided by the fentanyl was not being reversed. Furthermore, the long time between antagonism and administration of the first analgesic postoperatively certainly indicates the absence of pain in the immediate postoperative period following nalbuphine.

Moreover, the lack of increase in plasma norepinephrine is additional evidence that the patients experienced no pain during the observation period, since, as we previously reported, pain increases norepinephrine levels (15). In that earlier paper, we studied 80 patients who had recovered from enflurane anes-

Table 2. Ventilatory Changes after Antagonism of Fentanyl-Induced Ventilatory Depression by Nalbuphine

	15 min^{a} prior to nalbuphine	0 min	15 min after nalbuphine	30 min after nalbuphine	45 min after nalbuphine	60 min after nalbuphine
Minute volume (ml/min)	8,150.8 ± 1,092.6	1,479.5 ± 383.6^{d}	10,598.0 ± 1,185.5^{g}	10,919.0 ± 989.6^{g}	11,494.0 ± 898.9^{g}	10,517.0 ± 791.1^{g}
Tidal volume (ml)	575.4 ± 44.2	351.6 ± 92.8	577.4 ± 56.4	556.0 ± 51.7	620.0 ± 45.9^{f}	587.7 ± 35.0^{f}
Respiratory rate (breaths/min)	14.5 ± 2.3	5.1 ± 1.2^{d}	18.8 ± 1.6^{g}	20.4 ± 2.0^{g}	19.3 ± 2.0^{g}	17.8 ± 1.4^{g}
Pa_{O_2} (mm Hg)	135.3 ± 6.9	NA	173.1 ± 27.7	131.7 ± 11.3	142.1 ± 12.0	137.6 ± 12.0
Pa_{CO_2} (mm Hg)	38.6 ± 3	56.3 ± 2^{d}	44.3 ± 1^{g}	49.4 ± 7	41.5 ± 1^{g}	42.1 ± 1^{g}
pH	7.41 ± 0.03	NA	7.34 ± 0.01	7.34 ± 0.01	7.35 ± 0.01	7.36 ± 0.01
BE (mEq/L)	−0.1	NA	−1.8	−3.2	−3.0	−1.6

[a] Ventilation was still manually assisted.

Compared with −15 min: $^{b}P \le 0.05$, $^{c}P \le 0.01$, $^{d}P \le 0.001$.

Compared with 0 min: $^{e}P \le 0.05$, $^{f}P \le 0.01$, $^{g}P \le 0.001$.

Table 3. Pain Scores after Antagonism of Fentanyl by Nalbuphine

Pain scores^{a}	After antagonism			
	15 min	30 min	45 min	60 min
Mean	1.4	1.0	0.8	0.8
± SEM	0.9	0.6	0.5	0.5

[a] Pain scores on an analogue scale of 0–10.

thesia unsupplemented by analgesics and who had pain scores greater than 7 on an analogue pain scale of 0–10, and found markedly elevated concentrations of plasma norepinephrine and cortisol. The lack of increase in cortisol concentrations after the antagonism by nalbuphine in the present study indicates that no postoperative stress occurred in our patients. Hence, the patients in the present study had no subjective experience of pain, since pain is usually associated with an increased adrenocortical response as reflected in increased plasma free cortisol levels. The present data do not indicate whether the fentanyl-induced analgesia persisted after antagonism of its respiratory depressant effect or whether nalbuphine per se provided analgesia. This question requires further study.

The significant increase in mean epinephrine concentrations in the present study might have resulted from the combination of increased sympathetic activity associated with extubation and/or shivering and restlessness that occurred in some patients after extubation and transport to the recovery room. A similar hemodynamic response to antagonism of respiratory depression of fentanyl by nalbuphine in some cardiac patients has also been reported by Moldenhauer et al. (6). The increased hemodynamic response in combination with shivering and increased motor activity may explain the mean of 49 mm Hg CO_2 level found in our study (see Table 2) and the 47 mm Hg reported by Tabatabai et al. (7).

The dose of nalbuphine utilized in our study, 0.22 mg/kg, exceeded the dose of 0.1 mg/kg that has been reported to be effective for full antagonism of respiratory depression caused even by large doses of fentanyl (6,7). The reason for this lies in differences in methods. Both Moldenhauer et al. (6) and Tabatabai et al. (7) used incremental doses of nalbuphine of less than 0.1 mg/kg without a rigid time frame, in contrast to our fixed dosage schedule. We aimed at achieving prompt and complete antagonism of the fentanyl-induced respiratory depression followed by extubation within the first 15 min; hence, we gave several additional incremental doses of 0.1 mg/kg nalbuphine to the patients who were not promptly antagonized at 3 and 6 min according to our fixed time schedule. Some of these doses might have been unnecessary and in excess of doses required for full antagonism, since our protocol did not allow sufficient time for the development of a complete drug effect. Since the completion of this study, we have utilized only 30 μg/kg of nalbuphine incrementally in clinical practice and seldom require more than two or three doses, totaling 0.1 mg/kg. Despite the adequate antagonism of the fentanyl-induced respiratory depression in our study, the higher than normal Pa_{CO_2} we observed and that reported by others (7), emphasize the need for careful observation of the ventilatory status of the patient after reversal since renarcotization may occur, as Moldenhauer et al. (6) have observed. The hemodynamic status of the patients should also be carefully watched, since increases in blood pressure (7) and plasma epinephrine levels as shown in our study may occur in some patients.

In conclusion, nalbuphine promptly and effectively antagonizes the respiratory depression caused by fentanyl. The lack of increases in plasma levels of norepinephrine or cortisol and the absence of increases in mean analogue pain scores above 1.5 after nalbuphine administration indicate that either the analgesic effect of fentanyl remained unaffected or nalbuphine itself provided analgesia for the postoperative pain. No adverse circulatory changes or histamine release took place during this antagonism.

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The Pattern of Train-of-Four Fade after Atracurium:
Influence of Different Priming Doses

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NAGUIB M, ABDULATIF M, GYASI HK, KHAWAJI Y, ABSOOD GH. The pattern of train-of-four fade after atracurium: influence of different priming doses. Anesth Analg 1987;66:427–30.

This study was designed to investigate the effect of three different priming doses of atracurium—0.06, 0.07, and 0.08 mg/kg—followed 3 min later by the remainder of a 0.5 mg/kg dose on the relationship between the depression in the first twitch of the train-of-four (T1) and train-of-four (TOF) fade. This relationship was studied after the administration of the full dose of the relaxant in all groups. Of all the priming doses, 0.08 mg/kg atracurium, when followed 3 min later by 0.42 mg/kg atracurium, had a significantly greater fade in the TOF ratio at any given T1 value. This may indicate significant prejunctional activity. Acceleration of the onset of neuromuscular blockade was, however, evident in all groups that received atracurium in divided doses. The implication is, therefore, that prejunctional activity may not contribute significantly to the acceleration of onset of neuromuscular blockade after administration of atracurium in divided doses, as described in this study.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium.

The "priming principle" refers to the administration of a small (subparalyzing) dose of a nondepolarizing muscle relaxant a few minutes before the administration of the larger (intubating) dose (1). The onset of neuromuscular blockade can be accelerated by this maneuver (2–6). The priming dose is expected to occupy some of the prejunctional and/or postjunctional receptors at the neuromuscular junctions without blocking neuromuscular transmission, but subsequent doses will have a more rapid and more profound effect (7).

Bowman (8) suggested that the single twitch depression and train-of-four (TOF) fade are independent effects of neuromuscular blocking drugs, the former being the result of postjunctional block and the latter arising from the action at prejunctional receptors. Current evidence suggests that atracurium impairs neuromuscular transmission at both presynaptic and postsynaptic sites in the region of the motor end plate (9,10). The extent of interaction of the priming doses of atracurium with the aforementioned binding sites has not been explored.

This study was designed to investigate the effects of different combinations of priming and intubating doses on the relationship between the depression in the first twitch of the TOF and TOF fade.

Methods

After institutional approval, 32 ASA physical status I or II patients undergoing elective surgical procedures were studied. All patients were free of neuromuscular, renal, or hepatic disease; none were taking drugs known to interfere with neuromuscular function. Informed consent was obtained. All patients were premedicated with diazepam 10–15 mg orally 90 min preoperatively.

An intravenous infusion of lactated Ringer's solution in 5% dextrose was established prior to induction of anesthesia. The ECG and nasopharyngeal temperature were monitored continuously by a Medishield M1 monitor. Blood pressure was measured every 5 min by an electronic oscillotonometer (Dinamap).

In all patients, anesthesia was induced with fentanyl 2 μg/kg and thiopental 5 mg/kg, and was maintained with 70% nitrous oxide in oxygen and incremental doses of fentanyl or thiopental, or both, as required to maintain stable balanced anesthesia. Ventilation was assisted using a face mask and circle absorption system to maintain normocapnia and end-

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Table 1. Demographic Data (n = 8 in Each Group)

	Age (yr)	Weight (kg)	Sex (M/F)
Group I	31 ± 4.9	61.2 ± 10.3	1/1
Group II	25.3 ± 4.7	59.8 ± 7.5	1/1
Group III	28 ± 6.7	61.7 ± 6.8	1/1
Group IV	27.2 ± 7.7	57.1 ± 11.2	1/1

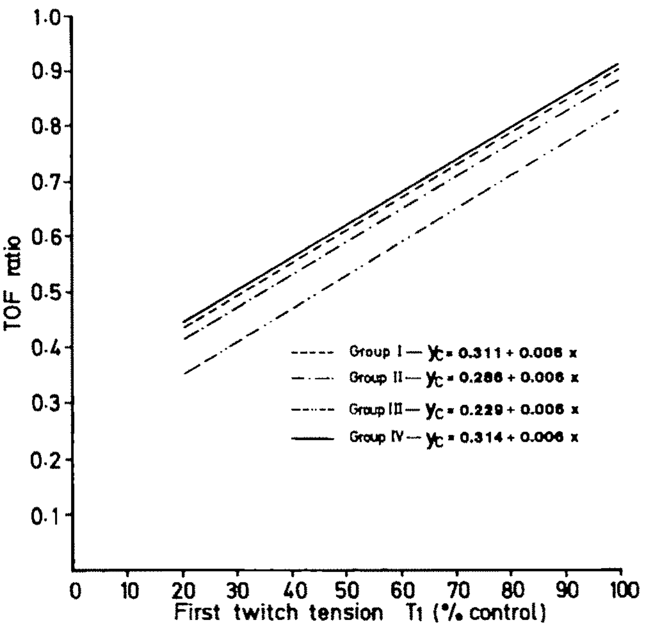

Figure 1. Relationship between the depression in T1 (percent of control) and TOF fade for the four groups studied (n = 8 in each). All patients received 0.5 mg/kg atracurium in either a single dose (group IV) or an initial dose of 0.06 (group I), 0.07 (group II), or 0.08 mg/kg atracurium (group III) followed 3 min later by the rest of the 0.5 mg/kg dose. The vertical distance for the regression line in group III was found to be significantly different ($P < 0.01$) from that in the other groups.

tidal CO_2 was monitored using a Datex infrared CO_2 analyzer.

After induction of anesthesia, the thumb of a restrained arm was attached to a force displacement transducer to record the response of the adductor pollicis to supramaximal stimulation of the ulnar nerve, using a Myotest peripheral nerve stimulator (Biometer) and a neuromuscular function analyzer with a continuous pen and paper recorder (Myograph 2000 Biometer) (11). The preload tension on the thumb was maintained at 300 g throughout the investigation.

Four square-wave impulses of 0.2 msec duration and 2-Hz frequency were repeated every 10 sec. After stabilization of the twitch recording, patients were assigned randomly to one of four groups (n = 8 in each). Stratified sampling was used to obtain an even sex distribution. The same total dose of atracurium, 0.5 mg/kg, was given to all patients. Atracurium was administered as an initial dose of 0.06 (group I), 0.07 (group II), or 0.08 mg/kg (group III) and followed 3 min later by the rest of the 0.5 mg/kg dose. In group IV (controls), atracurium was administered as a single bolus dose.

The TOF ratio (the amplitude of the fourth to the first evoked response; T4/T1) was recorded before administration of atracurium in all groups. The maximum effect of the priming dose on the TOF ratio was also recorded.

The TOF ratios were measured at 5% decrements of T1 evoked tension after the administration of the intubating (second) dose of atracurium in groups I, II, and III, and after the administration of the single dose in group IV.

Onset time (time from the end of injection of the intubating dose to the development of complete depression of all four responses to TOF stimulation) was determined. Tracheal intubation was performed immediately after complete TOF suppression in all groups.

Statistics

The individual values of TOF ratios after administration of the second dose of atracurium in groups I, II, and III and after administration of the single dose in group IV were utilized for linear regression analysis. The independent and dependent variables, respectively, were T1 and TOF ratio. Linearity of the regression lines was confirmed by the analysis of variance test for linearity (12). Then we tested the lines to determine if they deviated from parallelism. If they did not, the pooled slope, b, was calculated. Regression lines were compared using analysis of covariance. The relative positions of the lines were expressed by the calculation of a corrected mean value of y for each group. If the vertical distance between the parallel regression lines was found to be different, a t-test was applied to determine which lines differed in elevation (12).

Using analysis of variance, we compared mean age, body weight, and onset time among groups. A paired Student's t-test was applied to compare the TOF ratios before and after the administration of the priming dose in each group. For all statistical comparisons, differences were considered significant when $P < 0.01$.

Results

Results are expressed as means ± SD. There were no significant differences among the four groups with respect to age and body weight (Table 1).

Table 2. Effect of Priming Dose on TOF Ratios

		TOF ratios		
Group[a]	Priming dose (mg/kg)	Maximum effects of priming dose	P^b	Onset time (secs)
I	0.06	0.94 ± 0.05	0.047	76.5 ± 20.7[c]
II	0.07	0.94 ± 0.02	0.003	64.3 ± 22[c]
III	0.08	0.86 ± 0.07	0.002	77.2 ± 16.4[c]
IV	–	–	–	137.1 ± 38.5

[a] $n = 8$ in each group.
[b] Student's t-test, when compared with TOF ratios before injection of the priming doses.
[c] Onset times were significantly ($P < 0.01$) faster in the groups given atracurium in divided doses.

The TOF ratio decreased significantly to 0.94 ± 0.02 and 0.86 ± 0.07 after the priming doses in groups II and III, respectively (Table 2). The reduction in the TOF ratio after priming with 0.06 mg/kg in group I was not statistically significant ($P = 0.047$).

The mean onset times were 76.5 ± 20.7, 64.3 ± 22, and 77.2 ± 16.4 sec in groups I, II, and III, which received atracurium in divided doses (Table 2). This was significantly faster than it was in patients in the control group who were given the same dose of atracurium as a single bolus injection.

The test of difference between slopes indicated that the regression lines did not deviate from parallelism. The common slope was highly significant ($P = 5.4 \times 10^{-11}$). The pooled slope, b, was estimated to be 0.006. Analysis of covariance yielded a significant difference in the positions of the lines. Figure 1 demonstrates the relative positions of the lines after the calculation of the corrected mean value of y (TOF ratio) for each group. These parallel lines (Fig. 1) were drawn through the mean points, each with the same slope, b.

The common slope equations for all groups are:

Group I: $Y_c = 0.311 + 0.006x$
Group II: $Y_c = 0.286 + 0.066x$
Group III: $Y_c = 0.229 + 0.006x$
Group IV: $Y_c = 0.314 + 0.006x$

The subscript c is used to indicate that the predicted values Y_c were obtained using the common slope b.

The vertical distance for the regression line in group III was found to be significantly different from that in the other groups.

Discussion

Nondepolarizing muscle relaxants have both pre- and postjunctional blocking effects (8–10). The prejunctional action consists of blockade of a population of nicotinic autoreceptors that are normally activated by the transmitter (acetylcholine) and that serve to mediate mobilization of reserve transmitter to the readily releasable form within the terminal axoplasm (13). It is believed that these prejunctional autoreceptors function in a positive feedback control system that is activated by the transmitter itself and that serves to maintain availability of acetylcholine when demand for it is high (8,13). There is evidence that prejunctional receptors control an ion channel that is specific for sodium (14). Sodium is essential for the synthesis and mobilization of the transmitter but is not directly involved in the release process itself (14). Standaert suggested that fade may be due to blocking of cholinergic sodium channels in the nerve ending (15). Nevertheless, whether the nondepolarizing relaxants occupy the prejunctional receptors or block sodium channels, the end result is the same—that is, diminishing the release of acetylcholine from nerves stimulated at high frequency (14).

In this study, the same total dose of atracurium, 0.5 mg/kg, was given to all patients. Therefore, we would predict that after administration of the total dose of atracurium, the relationship between T1 and the TOF ratio at a given degree of neuromuscular block would be constant and would not vary with the method of drug administration. However, this was not the case. Therefore, the difference in the TOF ratio and T1 relationships may reflect a difference in pre- and postjunctional influences of the priming doses on the intubating doses. If this interpretation is correct, the different priming doses studied (0.06, 0.07, and 0.08 mg/kg atracurium) appeared to have different affinities for the prejunctional and postjunctional receptors. Of all the priming doses, only 0.08 mg/kg significantly affected the prejunctional activity of the intubating dose. This might indicate that the prejunctional activity of the priming doses is dose related, being evident only with higher doses.

Doherty et al. (5) observed no prejunctional activity after administration of pancuronium in an initial dose of 0.007 mg/kg followed 3 min later by 0.063 mg/kg. Hughes and Payne (16) studied the effect of atracurium on TOF and tetanic stimulation in humans. They reported that the fade of the fourth response of the TOF in the presence of atracurium was greater than that produced in tetanic response.

The present study was not designed primarily to assess the effect of the method of drug administration on the rate of onset of neuromuscular block. Nevertheless, our results confirm that administration of atracurium in divided doses has a more rapid onset of action than the single bolus injection, as reported previously (1–3,5–7). The acceleration of onset of neuromuscular blockade was evident in all groups that received atracurium in divided doses, but the prejunctional activity was significant only in group III. The implication, therefore, is that prejunctional activity did not contribute significantly to the acceleration of the onset of neuromuscular blockade. Further support should come from intracellular recording techniques in which the effect of the priming dose on the amplitude and frequency of the miniature end-plate potential can be obtained.

It has been shown that 70–75% of the end-plate receptors must be occupied by relaxant before the TOF ratio is affected (17). In this study, priming doses in the range of 0.07–0.08 mg/kg were associated with small but statistically significant reductions in the TOF ratios.

The present results indicate that after administration of atracurium as a single dose of 0.5 mg/kg or in an initial (priming) dose of 0.06 or 0.07 mg/kg followed 3 min later by the rest of the 0.5 mg/kg dose, the relationship between the depression of T1 and TOF fade at a given degree of neuromuscular blockade was not significantly different. In contrast, administration of 0.08 mg/kg atracurium followed 3 min later by 0.42 mg/kg atracurium resulted in a significantly greater fade in the TOF ratio at any given T1 value. This indicates that of all the priming doses studied (0.06, 0.07, and 0.08 mg/kg atracurium), the last dose significantly affected the prejunctional activity of the intubating dose. As the acceleration of onset of the neuromuscular blockade was evident in all groups that received atracurium in divided doses, it can be concluded that this prejunctional activity did not contribute significantly to the acceleration.

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Changes in Anterior Fontanel Pressure in Preterm Neonates Receiving Isoflurane, Halothane, Fentanyl, or Ketamine

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FRIESEN RH, THIEME RE, HONDA AT, MORRISON JE. Changes in anterior fontanel pressure in preterm neonates receiving isoflurane, halothane, fentanyl, or ketamine. Anesth Analg 1987;66:431–4.

The effects of anesthetics on intracranial pressure (ICP) may be different in preterm neonates than in adults because the neonate's cranial sutures are not yet fused. The authors monitored changes in anterior fontanel pressure (AFP), a noninvasive indicator of ICP, during anesthesia in 44 preterm neonates without neurologic disease. Atropine, 0.02 mg/kg, and pancuronium, 0.1 mg/kg, were given intravenously to all patients, who were ventilated with oxygen and air. Anterior fontanel pressure was monitored and recorded continuously with a Ladd AFP monitor. Systolic blood pressure (SAP) and mean blood pressure (MAP) were recorded at 1-min intervals. After a 5-min control period of stable AFP, each of the four groups of 11 patients then received either 0.75% isoflurane, 0.5% halothane, 20 μg/kg fentanyl, or 2 mg/kg ketamine. Anterior fontanel pressure decreased 11% during isoflurane administration, 9% during halothane administration, 10% after fentanyl, and 10% after ketamine. These changes were statistically significant, but clinically mild, and AFP remained within the normal range. Statistically significant decreases in SAP and MAP occurred during isoflurane and halothane administration, but not after fentanyl or ketamine. The authors conclude that indirectly measured ICP decreases slightly in preterm neonates without neurologic disease after administration of the anesthetics studied. The difference between these results and those of studies of ICP in adults is presumably due to the compliance of the neonate's open-sutured cranium.

Key Words: BRAIN—intracranial pressure. ANESTHESIA—pediatric. ANESTHETICS, VOLATILE.

The effects of anesthetic drugs on intracranial pressure (ICP) have been documented in adult patients with and without neurologic disease and in animals (1–8). Conclusions of these studies may not be applicable to preterm neonates for two reasons. First, the preterm neonate is physiologically immature and has different neurologic (9) and cardiovascular (10) responses than the older infant and adult. Second, the open sutures of the neonate's cranium are an anatomic feature not present in the subjects of previous studies.

It is desirable to document the effects of anesthetics on ICP in preterm neonates because intraventricular hemorrhage (IVH), a serious and common occurrence in preterm neonates (11–13), has been suggested as being associated with the perioperative period (14,15). Furthermore, preterm neonates with hydrocephalus or IVH who require anesthesia may already have elevated ICP and could be at risk for neurologic deterioration. Accordingly, this study was undertaken to document changes in anterior fontanel pressure (AFP), an indirect monitor of ICP, in preterm neonates during general anesthesia using isoflurane, halothane, fentanyl, or ketamine.

Methods

Forty-four preterm neonates (conceptual age less than 37 weeks; weight less than 2500 g) requiring a variety of surgical procedures were studied prospectively by methods approved by the institutional review board. All patients were ASA physical status 3 or 4. None of the patients had neurologic disease, were receiving vasoactive or inotropic drugs, or were given preanesthetic medication. Characteristics of the patient population are shown in Table 1. Conceptual age ranged from 26–36 weeks; weight ranged from 640 to 2250 g. The four groups were similar.

We measured AFP with the Ladd monitor (Ladd Research Industries, Inc., Burlington, VT). This pressure transducer was designed for noninvasive ICP

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Table 1. Patient Population

	Isoflurane	Halothane	Fentanyl	Ketamine
Postnatal age (day)	19.4 ± 20.7	10.5 ± 4.3	12.8 ± 15.9	15.7 ± 14.9
Conceptual age (wk)	33.2 ± 2.5	31.5 ± 3.0	30.6 ± 2.5	30.2 ± 3.3
Weight (g)	1541 ± 414	1281 ± 467	1157 ± 344	1198 ± 418
Urine specific gravity	1.011 ± 0.006	1.005 ± 0.002	1.007 ± 0.003	1.008 ± 0.003

Values are mean ± SD; n = 11 in each group.

monitoring and uses a fiberoptic sensor and a pneumatic tube and bellows operating on the applanation principle. The principle and the monitor have been previously described (16–18). Acceptable accuracy and correlation with directly measured ICP have been demonstrated (16,19–21).

On arrival in the operating room, monitoring devices were applied, the patient's scalp over the anterior fontanel was shaved, and tincture of benzoin was applied to the surrounding skin. Because application force of the Ladd sensor can affect the accuracy of its measurements (22,23), we used the application technique described by Hill and Volpe (20). This technique, using adhesive foam to secure the sensor over the anterior fontanel, is both accurate and reliable (20). We used the Ladd 10004 sensor, the Ladd M1000 pressure monitor, and a Ladd recorder.

Atropine, 0.02 mg/kg, and pancuronium, 0.1 mg/kg, were administered intravenously. Ventilation with air and oxygen was controlled manually using a nonrebreathing system (Jackson Rees' modification of Ayre's T-piece) in such a way that transcutaneous P_{CO_2} (Novametrix Medical Systems, Inc., Wallingford, CT) was maintained around 35 mm Hg. $F_{I_{O_2}}$ was adjusted to maintain Sa_{O_2} (Nellcor, Hayward, CA) between 90–92%.

Heart rate (HR), systolic blood pressure (SAP), and mean blood pressure (MAP) were measured and recorded at 1-min intervals with a Dinamap 847 monitor and printer (Critikon, Inc., Tampa, FL).

After the monitors were applied and the atropine and pancuronium were given, radiant heating devices maintained the patients' temperatures while AFP was observed. The patients were not moved or otherwise disturbed during this time, which was designated the baseline period. After AFP had been stable for 5 min, the patients were divided into four groups of 11 patients each using a table of random numbers. Group 1 received inhalation isoflurane 0.75%. Group 2 received inhalation halothane 0.5%. Group 3 received 20 μg/kg fentanyl intravenously. Group 4 received 2 mg/kg ketamine intravenously.

Anterior fontanel pressure was monitored for 10 min after anesthetic administration. During this time, controlled ventilation was maintained, but the patients were not otherwise moved or touched. After 10 min, the patients were positioned and prepared for operation, and data collection for the study ceased.

All but six patients (three in group 1, one each in groups 2, 3, and 4) had endotracheal tubes in place prior to the study. The six unintubated patients were ventilated by mask after pancuronium administration and during the 10 min after anesthetic administration; they were intubated only after data for the study had been collected. The mask was gently applied to the patients' faces without head movement to avoid affecting AFP measurement. Intravenous fluids and infusion rates were maintained at preoperative levels, which varied according to the patients' diseases and preoperative conditions.

Statistical analysis of the data was carried out using repeated measures analysis of variance. Statistical significance was assumed when $P < 0.05$.

Results

The results are displayed in Table 2. Anterior fontanel pressure decreased 11% during administration of 0.75% isoflurane, 9% during administration of 0.5% halothane, 10% after administration of 20 μg/kg fentanyl, and 10% after administration of 2 mg/kg ketamine. These changes were statistically significant ($P < 0.05$). There were no significant differences among the groups in either absolute AFP values or their changes.

Statistically significant decreases in SAP and MAP occurred during administration of isoflurane and halothane, but not after fentanyl or ketamine. The differences among the groups in SAP and MAP levels were not statistically significant.

Discussion

The results of this study demonstrate that administration of isoflurane, halothane, fentanyl, or ketamine during controlled ventilation to preterm neonates without neurologic disease causes a slight decrease in AFP. The decrease in AFP in each group was statistically significant. Because AFP is a reliable indicator of ICP (16,19–21), we conclude that administration of these anesthetics results in a mild decrease in ICP in preterm neonates.

Table 2. Changes in Anterior Fontanel Pressure, Systolic Blood Pressure, and Mean Blood Pressure during Anesthesia in Preterm Neonates

	Isoflurane	Halothane	Fentanyl	Ketamine
Baseline AFP (cm H_2O)	6.5 ± 2.8	5.4 ± 1.3	6.1 ± 1.9	7.3 ± 2.7
Anesthesia AFP	5.8 ± 2.9*	4.9 ± 1.5*	5.5 ± 1.9*	6.6 ± 2.4*
Percent change	−11	−9	−10	−10
Baseline SAP (mm Hg)	62 ± 13	56 ± 15	56 ± 19	56 ± 14
Anesthesia SAP	55 ± 13*	46 ± 13*	49 ± 19	53 ± 14
Percent change	−11	−18	−13	−5
Baseline MAP (mm Hg)	52 ± 12	45 ± 14	46 ± 16	44 ± 11
Anesthesia MAP	43 ± 11*	35 ± 10*	37 ± 15	42 ± 10
Percent change	−17	−22	−20	−4
$Ptcco_2$ (mm Hg)	34 ± 5	36 ± 4	35 ± 6	34 ± 6

Abbreviations: AFP, anterior fontanel pressure; SAP, systolic blood pressure; MAP, mean arterial pressure, $Ptcco_2$, transcutaneous pressure of CO_2.
Values are mean ±SD; $n = 11$ in each group.
*Significantly different from baseline ($P < 0.05$) by repeated measures analysis of variance.

The results of this study are similar to those of studies of fentanyl in adult neurosurgical patients. In those studies, fentanyl, in combination with droperidol, was associated with a decrease in ICP during normocapnia (3,4).

However, these results are not consistent with most data from previously published studies of the other anesthetics in adults and animals. Isoflurane increased ICP significantly in normal cats and adult neurosurgical patients during normocapnia (7,8), but not in neurosurgical patients during hypocapnia (7). Halothane caused a significant increase in ICP in both normal and neurosurgical patients (1,2), which was attenuated by prior establishment of hypocapnia (2). Administration of ketamine to normal and neurosurgical adult patients also resulted in significant increases in ICP (5,6). None of these anesthetics caused an increase in AFP during normocapnia in our preterm neonates.

The apparent explanation for the differences between our results and those of the adult studies lies in the fact that the neonate's cranial sutures are not fused. Thus, the increase in cerebral blood volume observed after halothane and ketamine (24) results in an increase in ICP in the noncompliant closed cranium of the adult, but not in the compliant open cranium of the neonate.

The mechanism of the decrease in AFP that we observed in our patients cannot be explained by our data. Although the decreases in AFP were statistically significant, they were small and are probably of little clinical significance. The clinical importance of the results lies in the observation that AFP did not increase significantly after isoflurane, halothane, and ketamine, as ICP does in adults (1,2,5–8).

The data suggest that administration of the described doses of isoflurane, halothane, fentanyl, or ketamine does not introduce another risk factor for the development of IVH to neurologically normal preterm neonates. Although IVH is a multifactorial problem (13,25), suggestions that the perioperative period is one of greater risk for the development of IVH have been made (14,15) and refuted (26). Among the many factors associated with IVH are three which are of particular note in this context: changes in SAP of greater than 100% (25), fluctuations in cerebral blood flow (CBF) velocity of greater than 30% (27), and increased AFP (21,28). The anesthetics used in this study do not cause SAP changes of that amount (29), and the use of pancuronium has been shown to eliminate fluctuations in CBF velocity (27). The present study, therefore, adds further evidence that the anesthetic drugs described are safe to use with regard to development of IVH.

Another clinical implication of this study is the suggestion that perhaps none of the four anesthetics studied is contraindicated in preterm neonates with neurologic diseases, such as IVH or hydrocephalus, which may be accompanied by increased ICP. However, the open cranial sutures of preterm neonates can be expected to accommodate only a limited increase in intracranial volume before loss of compliance occurs, so we cannot support this suggestion. Studies of AFP changes during anesthesia in preterm neonates with neurologic disease should answer this question.

We conclude that administration of isoflurane, halothane, fentanyl, or ketamine to preterm neonates without neurologic disease is associated with a slight decrease in indirectly measured ICP. This study demonstrates that significant differences in the effects of anesthetics on ICP exist between preterm neonates and adults. Further studies are recommended to evaluate changes in AFP during anesthesia of preterm neonates with neurologic disease.

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Plasma Concentrations of Epidural Bupivacaine in Mother and Newborn:

0.125% versus 0.375%

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VAN ZUNDERT A, BURM A, VAN KLEEF J, SPIERDIJK J, VAN DER AA P, SMOLDERS F, VAES L, DE WOLF A. Plasma concentrations of epidural bupivacaine in mother and newborn: 0.125% versus 0.375%. Anesth Analg 1987;66:435–41.

Central venous plasma concentrations of bupivacaine were determined in two groups of 15 parturients each who were given epidural analgesia for labor and vaginal delivery. One group received 10 ml of 0.125% bupivacaine plus epinephrine 1:800,000, the other group received 7 ml of 0.375% bupivacaine plus epinephrine 1:800,000. Plasma concentrations of bupivacaine in the umbilical venous (UV) and the umbilical arterial (UA) blood of their babies were also determined. The mean UA, UV, and maternal central venous (MV) plasma concentrations of bupivacaine differed significantly between the two groups: in patients given 0.375% bupivacaine UA values were 63% higher ($P < 0.01$), UV values were 57% higher ($P < 0.01$), and the MV values were 34% higher ($P < 0.05$) than in patients given 0.125% bupivacaine. The measured plasma concentrations speak in favor of the less concentrated solution of bupivacaine in epidural analgesia for obstetrics. Seven milliliters of bupivacaine 0.375% is suitable for epidural analgesia in obstetrics but a low concentration–low dose technique, using 10 ml of bupivacaine 0.125% plus epinephrine 1:800,000 is safer. It provides good analgesia with minimal or no motor block and is associated with low maternal and neonatal plasma concentrations of bupivacaine, well below toxic levels and, to our knowledge, lower than in any other study.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—epidural.

Several authors have reported good results from using 0.125% bupivacaine plus epinephrine 1:800,000 for epidural analgesia for labor and vaginal delivery (1–4). Nevertheless the most widely used concentrations of bupivacaine used in obstetrics range from 0.25% to 0.5%. Many studies of the use of bupivacaine in obstetrics have included measurements of concentrations of bupivacaine in mother and newborn associated with epidural analgesia for childbirth (2,5–24) (Table 1). However, most of these measurements were made by means of peripheral venous samples and/or whole blood samples, both of which may give lower values than central venous plasma concentrations (25).

To see if we could obtain lower maternal and fetal plasma concentrations with a low concentration–low dose technique and yet provide good analgesia, in our study we determined central venous plasma concentrations of bupivacaine in parturients during labor and at the moment of vaginal delivery. We also measured arterial and venous cord samples of the newborns immediately after delivery. The results of epidural analgesia with 0.125% bupivacaine and 0.375% bupivacaine, both containing epinephrine 1:800,000, were compared.

Materials and Methods

After informed consent was obtained, a prospective randomized study for determination of plasma concentrations of bupivacaine was performed in 30 unselected women who presented for labor and vaginal delivery under epidural analgesia.

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Table 1. Plasma Concentrations of Bupivacaine in Obstetric Epidural Anesthesia

Reference	Year	Number of patients	Concentration of bupivacaine	Epinephrine	Mean dose per injection (mg)	Mean total dose (mg)	Mean plasma concentrations at delivery (ng/ml)			
							Mother	UA	UV	UV/MV ratio
Vaginal deliveries: intermittent technique										
Thomas et al. (5)	1969	12	0.5%	1:200,000	50	69	260 VP	—	110 P	0.43
Reynolds and Taylor (6)	1970	23	0.5%	1:200,000	—	121	260 VB	—	80 B	0.31
Reynolds and Taylor (7)	1971	9	0.5%	1:200,000	30–55	126	490 VP	—	180 P	0.40
Reynolds and Taylor (7)	1971	9	0.5%	—	30–40	128	670 VP	—	160 P	0.23
Hyman and Shnider (8)	1971	21	0.25/0.5%	1:200,000	—	57	220 AB	62 B	82 B	0.29 (UV/MA)
Hyman and Shnider (8)	1971	11	0.25/0.5%	—	—	83	390 AB	72 B	98 B	0.26 (UV/MA)
Hyman and Shnider (8)	1971	32	0.25/0.5%	1:200,000	—	96	240 AB	65 B	82 B	0.38 (UV/MA)
Reynolds et al. (9)	1973	30	0.5%	1:200,000	46.6	126.3	360 VP	—	88 P	0.26
Reynolds et al. (9)	1973	30	0.5%	—	47.7	147	540 VP	—	140 P	0.28
Geerinckx et al. (2)	1974	19	0.125%	1:400,000	12.5	66	154 VP	35 P	44 P	0.28
Belfrage et al. (10)	1975	33	0.25%	1:200,000	15–20	62	185 VB	48 B	51 B	0.27
Thomas et al. (11)	1976	31	0.5%	1:200,000	—	107	410 VB	100 B	110 B	0.27
Scanlon et al. (12)	1976	20	0.5%	—	—	112	950 VP	—	220 P	0.24
Zaaijman et al. (13)	1979	25	0.5%	1:200,000	—	81	177 VB	—	43 B	0.24
Fuchi and Noda (14)	1980	15	0.25%	—	12.5–17.5	42	345 VB	104 B	129 B	0.37
Abboud et al. (15)	1982	20	0.5%	—	—	—	310 VP	150 P	110 P	0.31
Vaginal deliveries: continuous technique										
Evans and Carrie (16)	1979	30	0.25%	—	23.7 mg/hr	85.2	319 VP	—	94 P	0.30
Rosenblatt et al. (17)	1983	97	0.25%	—	25.0 mg/hr	—	760 VP	—	170 P	0.22
Abboud et al. (18)	1984	23	0.125%	—	21.5 mg/hr	—	540 VP	150 P	180 P	0.33
Li et al. (19)	1985	20	0.0625%	—	19.2 mg/hr	165.2	328 VB	—	152 B	0.44
Li et al. (19)	1985	20	0.0625%	—	20.9 mg/hr	170.8	543 VB	—	122 B	0.45
Li et al. (19)	1985	19	0.125%	—	23.6 mg/hr	161	438 VB	—	159 B	0.41
Li et al. (19)	1985	20	0.125%	—	24.7 mg/hr	197.9	325 VB	—	103 B	0.37
Cesarean sections										
Magno et al. (20)	1976	14	0.75%	—	90–120	103	490 VB	—	210 B	0.41
McGuinness et al. (21)	1978	10	0.75%	—	165–184	168	720 AB	210 AB	170 B	0.25 (UV/MA)
Abboud et al. (22)	1983	16	0.75%	—	—	135	780 VP	170 P	210 P	0.27
Kileff et al. (23)	1984	19	0.5%	—	—	145	750 VP	240 P	270 P	0.36
Dutton et al. (24)	1984	16	0.5%	1:200,000	—	112.7	850 VP	—	170 P	0.21
Dutton et al. (24)	1984	18	0.75%	1:200,000	—	144.9	950 VP	—	250 P	0.27

Abbreviations: UA, umbilical arterial; UV, umbilical venous; MV, maternal venous; A, arterial concentration; V, venous (peripheral) concentration; B, blood; P, plasma.

Table 2. Demographics of the Two Groups of Women Receiving Different Concentrations of Bupivacaine

Parameter	Percent bupivacaine	Mean ± SE	Median	*P*
Maternal age (years)	0.375	26.0 ± 0.6	25.0	>0.05
	0.125	25.9 ± 1.0	26.0	
Maternal weight (kg)	0.375	67.4 ± 2.4	69.0	>0.05
	0.125	70.4 ± 2.7	70.0	
Parity	0.375	1.67 ± 0.21	1.0	>0.05
	0.125	1.60 ± 0.16	2.0	
Duration of analgesia (min)	0.375	194.0 ± 26.0	165.0	>0.05
	0.125	182.0 ± 20.0	195.0	
Last-dose-delivery time (min)	0.375	63.9 ± 8.9	52.0	>0.05
	0.125	47.5 ± 7.4	38.0	
Expulsion time (min)	0.375	5.1 ± 0.7	5.5	>0.05
	0.125	5.1 ± 0.8	5.0	
Baby's weight (g)	0.375	3230.0 ± 133.0	3150.0	>0.05
	0.125	3383.0 ± 111.0	3350.0	
Apgar score (1 min)	0.375	7.8 ± 0.6	9.0	>0.05
	0.125	8.5 ± 0.3	9.0	
Apgar score (5 min)	0.375	9.1 ± 0.2	9.0	>0.05
	0.125	9.4 ± 0.2	10.0	

Epidural analgesia was performed in two unselected groups of 15 women each with either bupivacaine 0.125% plus epinephrine 1:800,000 or with bupivacaine 0.375% plus epinephrine 1:800,000. Excluded were parturients in whom labor lasted more than 7 hr because we judged the amount of blood to be taken for samples to be excessive. In group 1, 10 ml (12.50 mg) bupivacaine 0.125% plus epinephrine 1:800,000 was used, in group 2, 7 ml (26.25 mg) bupivacaine 0.375% plus epinephrine 1:800,000 was used.

After injection maternal heart rate was monitored continuously by palpation of the radial pulse for 2 min and blood pressure was measured for 10 min. Fetal heart rate was monitored continuously by fetal scalp electrodes. Uterine contractions were also continuously registered.

All mothers were given an intravenous infusion of 5% glucose in physiologic saline at a minimum rate of 200 ml/hr during labor and delivery. Labor began spontaneously in 67% of the cases. No woman received other medications except for the infusion of 1–8 mU/min of oxytocin in 23 patients. Extent of analgesia was assessed 20 min after each epidural injection, using the pinprick method. Supplemental doses of bupivacaine were given as needed to produce pain-free labor and delivery in all cases. Duration of analgesia was defined as the time between the first epidural injection of the local anesthetic and delivery. The expulsion time (ET) was the time from the first expulsion effort to delivery of the baby.

A central venous catheter was introduced into the superior vena cava via the basilic vein before epidural analgesia. Blood samples (3 ml each) were obtained via the central venous catheter after first withdrawing a volume exceeding the volume of the catheter. Samples were collected before the epidural injection and every 10 min after each epidural injection until delivery. At delivery, blood samples from the umbilical vein (UV) and umbilical artery (UA) were obtained before clamping the umbilical cord. At the same time, another maternal blood sample was taken.

Each sample was transferred into heparinized centrifuge tubes, which were sealed with plastic foil (Parafilm®) and stored in the refrigerator. Within 8 hr, plasma was obtained by centrifugation at 2500 × g for 10 min and stored at −20°C until the time of analysis.

Bupivacaine concentrations in plasma were determined by means of capillary gas chromatography. The gas chromatograph (Hewlett-Packard 5710) was equipped with a nitrogen detector (model 18789 A) and a SCOT column. Bupivacaine and an added internal standard were extracted from plasma with n-pentane. The extracted products were introduced into the gas chromatograph via a solid injection system. The combination of a support-coated open tubular column and a nitrogen-selective detector insures a good selectivity and a high sensivity. The coefficient of variation of the method at concentrations exceeding 3 ng of bupivacaine per milliliter of plasma is less than 6%. The detection limit is less than 1 ng/ml (26,27). In this study all plasma concentrations are expressed in terms of free base equivalents.

For each delivery, the mother's and baby's weights, parity, duration of analgesia, last dose-to-delivery time (LDD), and Apgar scores at 1 and 5 min were recorded.

The Mann–Whitney *U*-test was used to compare mean values between the two groups. A value of *P*

Table 3. Total Doses of Bupivacaine and Plasma Concentrations at Delivery

Parameter	Percent bupivacaine	Mean ± SE	Median	P
Total dose (mg)	0.375	66.5 ± 6.2	52.5	<0.0001
	0.125	42.1 ± 2.6	37.5	
Dose per hour (mg)	0.375	24.1 ± 2.8	20.5	<0.05
	0.125	16.5 ± 1.9	16.7	
Maternal vein (ng/ml)	0.375	307.0 ± 24.0	316.0	<0.05
	0.125	229.0 ± 19.0	239.0	
Umbilical artery (ng/ml)	0.375	57.0 ± 5.0	59.0	<0.01
	0.125	35.0 ± 3.0	33.0	
Umbilical vein (ng/ml)	0.375	69.0 ± 7.0	65.0	<0.01
	0.125	44.0 ± 3.0	45.0	
UA/MV ratio	0.375	0.19 ± 0.01	0.19	>0.05
	0.125	0.17 ± 0.02	0.19	
UV/MV ratio	0.375	0.224 ± 0.01	0.22	>0.05
	0.125	0.206 ± 0.02	0.23	

< 0.05 was considered as the minimum level of statistical significance.

Results

The two groups of women receiving different concentrations of bupivacaine were comparable in age, body weight, parity, duration of analgesia, last dose-to-delivery time, and expulsion time. Babies' weights and Apgar scores at 1 and 5 min were also comparable (Table 2).

Excellent analgesia was obtained in all cases. Eleven babies in the 0.125% and ten babies in the 0.375% group were delivered spontaneously. The others were delivered with the help of a vacuum extractor. The mean expulsion time in both groups was 5.1 min.

Table 3 shows the doses of bupivacaine administered and the resulting mean plasma concentrations in the mothers and newborns. The mean total dose given epidurally to parturients in the two groups differed significantly: 42.1 mg was given in the 0.125% group, whereas 66.5 mg was given in the 0.375% group. The dosage in the latter group was 58% greater. The mean dose per hour was 16.5 mg in the 0.125% group and 24.1 mg in the 0.375% group. The latter dosage is a statistically significant 46% greater.

The mean UA, UV, and maternal vein (MV) plasma concentrations of bupivacaine differed significantly in the two groups. In the 0.375% group, UA values were 63% higher, UV values were 57% higher, and the MV values were 34% higher than those in the 0.125% group of parturients. The UV concentration of bupivacaine was 21% greater than the concentration in the UA in the 0.375% group, and 26% greater in the 0.125% group.

The mean UA/MV ratio was similar in both groups: 0.19 in the 0.375% group and 0.17 in the 0.125% group. The mean UV/MV ratio, 0.22 in the 0.375% group, also was not significantly different from the 0.21 ratio in the 0.125% group.

Discussion

Systemic toxicity is always a potential hazard after administration of local anesthetic drugs into the epidural space, especially when there is accidental intravenous injection. Central nervous system effects have been demonstrated in humans with venous plasma concentrations of bupivacaine of 1500–4000 ng/ml (38).

Exact toxic plasma levels of bupivacaine in adults have, however, not yet been determined, and it is even more difficult to identify toxic levels of bupivacaine in the newborn. Therefore, we should keep the dose of local anesthetic drugs used in obstetrics as low as possible. In our study, bupivacaine concentrations were determined in central venous plasma samples. Although in most other studies (Table 1) the determination of circulatory blood levels of bupivacaine was performed using peripheral venous samples and/or whole blood, which results in relatively low values, UA and UV concentrations of bupivacaine lower than those in our study with 0.125% bupivacaine plus epinephrine 1:800,000 have never been demonstrated, to our knowledge. All plasma concentrations in this study were well below what is considered to be the toxic level in the mother (Table 4).

Our data also suggest there is only a moderate cumulative effect when repeated injections of bupivacaine are used (Fig. 1). This finding contrasts with the results from studies of other local anesthetic drugs (lidocaine and mepivacaine). These report a substantial accumulation of lidocaine and mepivacaine in blood after repeated epidural injections (6).

Table 4. Extremes of Plasma Bupivacaine Levels Found in Mothers and Neonates

	0.125 % group		0.375 % group		
	Extremes	Median	Extremes	Median	*P*
Maternal vein	40.3–387.0	239	67.5–802.0	316	<0.05
Umbilical artery	14.8–50.2	32.5	26.0–88.4	59.1	<0.01
Umbilical vein	23.7–59.6	45.4	31.2–111.0	64.6	<0.01

Units are ng/ml.

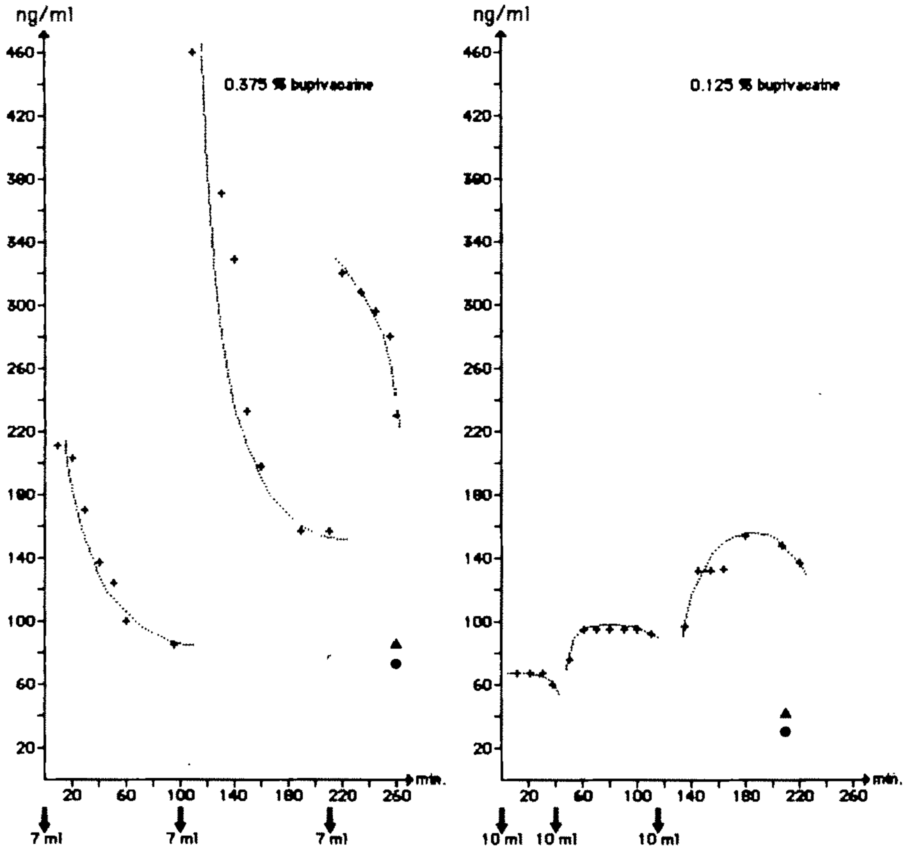

Figure 1. Typical examples of central venous plasma concentrations (ng/ml) of bupivacaine in a parturient receiving 0.375% bupivacaine + epinephrine 1: 800,000 (left), and in a parturient receiving 0.125% bupivacaine + epinephrine 1:800,000 (right). Arrows indicate the moment and amount of each injection. ▲, UV plasma concentration of bupivacaine in the umbilical vein. ●, UA plasma concentration of bupivacaine in the umbilical artery.

In our study, we found that the mean total dose and the mean dose per hour were 58% and 46% greater when 0.375% bupivacaine was used than when 0.125% bupivacaine was used. The mean UA and UV concentrations were thus 63% and 57% greater in the 0.375% group. Therefore, we advocate the use of the more dilute bupivacaine solutions.

The UA/MV and UV/MV ratios were independent of the concentration of the local anesthetic used, which confirms observations made by other investigators (Table 1). The mean plasma concentration of bupivacaine found in the umbilical vein is about 20% of that found in the venous plasma of the mother, both in our study and in the studies of other investigators (Table 1). The low fetal/maternal ratio of bupivacaine at birth is due to considerable uptake of bupivacaine by fetal tissues and is not due to diminished placental transfer, as demonstrated by Kuhnert et al. (29) in a study of the disposition of bupivacaine in mother, fetus, and newborn after epidural analgesia for cesarean sections. In this study the UA/MV and UV/MV ratios of bupivacaine were constant regardless of which concentration was used. If low concentrations of bupivacaine in the fetal tissues are important, it is worth striving for the lowest possible maternal plasma levels of bupivacaine. We found no relation between the UA/MV and UV/MV ratios and the last dose-to-delivery interval (Fig. 2), thus confirming earlier studies (2,6,7,9–11).

A price must be paid with regard to toxicity when a more concentrated solution is used and, consequently, when a larger dose of local anesthetic is in-

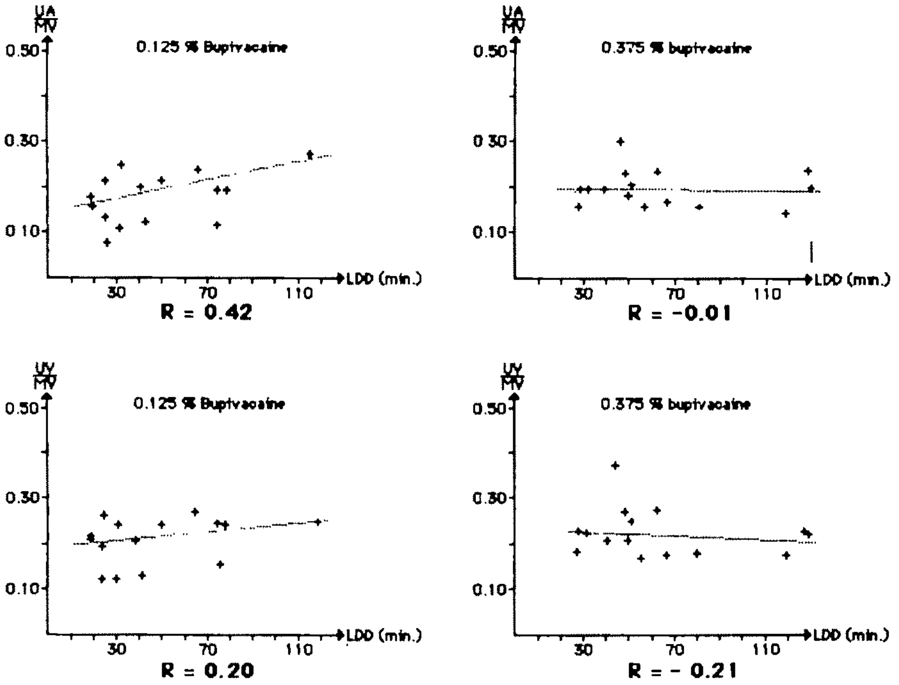

Figure 2. Relation between UA/MV and UV/MV ratios and the interval between the last dose and the delivery (LDD) ($P > 0.05$). The UA/MV and UV/MV ratios of both groups were independent of the last dose-to-delivery interval. *R*, correlation coefficient.

advertently injected into a vein (28) or in the subarachnoid space (30). The use of 0.75% bupivacaine in obstetrics has been criticized and its use is even forbidden in the U.S. (24).

We normally use 10 ml of 0.125% bupivacaine plus epinephrine 1:800,000. This is an effective dose and a test dose at the same time. Even 12.5 mg of bupivacaine is harmless if given inadvertently intrathecally (3). It is about what is needed to obtain spinal anesthesia, i.e., the equivalent of 3 ml of 0.5% bupivacaine (31–35).

Because epinephrine is added to the 0.125% solution, an inadvertent intravenous injection alerts the anesthesiologist by causing palpitations, tachycardia, and a temporary increase in blood pressure in the mother (36,37).

Seven mililiters of 0.375% bupivacaine is suitable for epidural analgesia, but a low-dose technique using 10 ml of 0.125% bupivacaine plus epinephrine 1:800,000 is safer in the case of an inadvertent intravenous or intrathecal injection. It also results in lower plasma concentrations in both mother and newborn.

In an attempt to use an even more diluted solution, i.e., 0.0625% bupivacaine at 10 ml/hr, Li et al. (19) were not able to provide a painless labor and delivery. They concluded that 0.125% bupivacaine is the optimal concentration for epidural analgesia in labor.

In conclusion, plasma concentrations of bupivacaine mandate the use of less concentrated solutions of bupivacaine in epidural analgesia for obstetrics. Epidural analgesia using 0.125% bupivacaine plus epinephrine 1:800,000 provides good analgesia during labor and vaginal deliveries, and yet is associated with maternal plasma concentrations of bupivacaine well below toxic levels as well as lower neonatal drug concentrations than more concentrated solutions. Furthermore, epidural analgesia with 0.125% bupivacaine is so safe that even inadvertent intravenous or intrathecal injection would be harmless.

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Prolongation of Isobaric Bupivacaine Spinal Anesthesia with Epinephrine and Clonidine for Hip Surgery in the Elderly

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RACLE JP, BENKHADRA A, POY JY, GLEIZAL B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987;66:442–6.

The effects of vasoconstrictors on the duration of isobaric bupivacaine spinal anesthesia are unknown. A prospective controlled study was conducted on 60 ASA class II or III patients aged 75 yr or more who were scheduled for spinal anesthesia for orthopedic hip surgery. The subjects were randomly allocated into three groups. All patients received 15 mg bupivacaine plain solution in 4 ml in the horizontal position. Group I patients received bupivacaine plus 1 ml normal saline; group II patients received bupivacaine plus 0.2 mg epinephrine; group III patients received bupivacaine plus 0.15 mg clonidine. The segmental level of sensory loss was tested using forceps.

In one case in group III, anesthesia was unsatisfactory. The time course required for maximal spread of the sensory blockade did not differ in the three groups. No difference was observed between mean highest levels of sensory anesthesia. The mean time to two-segment regression from the highest level was significantly longer in group III than in groups I and II. Mean time for regression to the L2 segment was also significantly longer in groups II and III than in group I. This time tended to increase more with the bupivacaine plus clonidine solution than with the bupivacaine plus epinephrine solution. Significant prolongation of motor block was also associated with the addition of clonidine.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine.

Isobaric bupivacaine produces reliable spinal anesthesia for orthopedic surgery in the elderly (1,2). In some cases, the duration of the surgical procedure exceeds the duration of a spinal anesthesia. Epinephrine 0.2 mg added to local anesthetic solutions prolonged the duration of anesthesia (3). This might be related to local vasoconstriction or to a direct analgetic effect of α-adrenergic agonists on the central nervous system (4).

Clonidine is well know to stimulate both peripheral and central alpha-2-adrenergic receptors (5). Thus, prolongation of the duration of spinal anesthesia might theoretically be expected with clonidine. After intrathecal administration, a marked analgetic effect of clonidine has been observed (6). A preliminary study in dogs indicates that clonidine, when used as an adjunct to tetracaine spinal anesthesia, was significantly more effective than epinephrine in prolonging sensory blockade (7).

The present study was undertaken to compare the efficacy of epinephrine and clonidine in prolonging isobaric bupivacaine spinal anesthesia for hip surgery in elderly patients.

Methods

Sixty patients over the age of 75 yr scheduled for hip surgery were studied. All were in ASA categories II–III. All patients gave informed oral consent after detailed explanation of the procedure. The patients were randomly allocated to three groups according to the permutation table of Cochran and Cox. Group I ($n = 20$) received 0.5% bupivacaine 3 ml (15 mg) plus 1 ml of 0.9% sodium chloride. Group II ($n = 20$) received 0.5% bupivacaine 3 ml plus 0.2 ml of 1:1000 epinephrine (0.2 mg) and 0.8 ml of normal saline. Group III ($n = 20$) received 0.5% bupivacaine 3 ml plus 1 ml of clonidine (0.15 mg). The epinephrine, clonidine, and normal saline were added at the time of injection. Patients' characteristics and duration of operations are shown in Table 1.

Premedication consisted of hydroxyzine 50–100 mg and atropine 0.01 mg/kg intramuscularly about 1 hr prior to anesthesia. Immediately before induction of anesthesia, an 18-gauge cannula was inserted into an arm vein and 300 ml of lactated Ringer's solution was

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Table 1. Mean (±SEM) Age, Weight, and Height of Patients and Duration of Operation in Each Group

Variables	Group I (bupivacaine + normal saline)	Group II (bupivacaine + 0.2 mg epinephrine	Group III (bupivacaine + 0.15 mg clonidine)
Sex			
Female	13	12	11
Male	7	8	9
Age (yr)			
Mean	82.7 ± 1.3	80.8 ± 1	79.1 ± 1.1
Range	75–93	75–87	75–87
Weight (kg)			
Mean	57.9 ± 2.7	66.3 ± 3.5	62.5 ± 2.7
Range	42–79	40–81	45–81
Height (cm)			
Mean	157.7 ± 2.1	162.6 ± 1.8	159.8 ± 1.8
Range	145–176	148–173	145–171
Duration of operation (min)			
Mean	88 ± 6	102 ± 9	96 ± 11
Range	50–160	60–210	60–210

infused. This was repeated 30 min after injection of the spinal anesthetic. The patients were placed in the lateral decubitus position, with the operative side uppermost. Under aseptic conditions, lumbar puncture was performed with a 22-gauge spinal needle at the L3–4 intervertebral space using either a midline or a paramedian approach. Before injection, a free flow of clear cerebrospinal fluid was ascertained during turning of the needle 90–180 degrees and then during aspiration of 0.2 ml. All injections were made at a rate of about 1 ml in 4–5 sec and all solutions were at room temperature when injected. Immediately after injection, the patient was placed in the supine horizontal position for the duration of surgery.

The time of completion of injection of the local anesthetic solution into the subarachnoid space was used as the basis for measurement of all time intervals. The dermatome levels of sensory anesthesia were evaluated by pinching bilaterally in a midclavicular line and on the legs with a Pean forceps at 2-min intervals for 30 min. Sensory anesthesia was considered complete when the patient did not respond to this forceps closed to its first rachet (3). When levels of anesthesia were not equal bilaterally, the higher level was used for statistical purposes.

If during surgery pain required supplementation with intravenous or inhalation anesthesia, anesthesia was considered unsatisfactory. Patients with unsatisfactory anesthesia were not included in the analysis of the variables studied. Motor blockade was assessed at the same time as sensory levels using criteria described by Bromage (8): 0 = no impairment of movement of legs and feet; 1 = barely able to flex knees, no impairment of movement of feet; 2 = unable to flex knees, barely able to move feet; 3 = unable to move feet or knees. Thereafter, anesthesia and motor block were assessed every 30 min until anesthesia had regressed to the point that the cutaneous response to clamping in the operative site was identical to that on the forearm or for a maximum of 5 hr after injection. The mean time to recovery from anesthesia in the two uppermost segments and the recovery of the L2 segment were noted.

Blood pressure and heart rate (sphygmomanometer Dinamap Critikon) were measured at 2.5-min intervals throughout anesthesia and surgery, and at intervals of 15 min during recovery. The ECG was monitored continuously during induction of anesthesia and during surgery. Hypotension was treated with intravenous fluids. If this measure did not prevent a decrease in systolic blood pressure greater than 30% below levels observed under resting conditions, intravenous ephedrine (15–30 mg) was used. Resting blood pressure was determined during the anesthesiologist's preoperative visit the day before surgery (9).

All data are presented as means ± SEM, together with ranges. Mean values were compared using one-way analysis of variance and appropriate Student's test. A value of $P < 0.05$ was considered statistically significant.

Results

There were no significant differences among the three groups with regard to sex, age, weight, and height of patients or duration of operations (Table 1). In one patient in group III, general anesthesia was necessary because of inadequate anesthesia despite apparently

Table 2. Sensory Levels After Intrathecal Administration of Bupivacaine with or without Vasoconstrictors (mean ± SEM)

	Group I	Group II	Group III
Highest level of anesthesia			
Mean	T10.5 ± 0.3	T9.1 ± 0.5	T10.7 ± 0.4
Range	T12–T7	T12–T5	L1–T6
Time from injection to highest level (min)			
Mean	9.5 ± 0.6	9.2 ± 0.9	9.9 ± 1.2
Range	6–18	4–22	4–22
Time for two-segment regression (min)			
Mean	108 ± 7	126 ± 12	171 ± 12^{b,d}
Range	60–225	60–225	75–240
Time for regression to L2 (min)			
Mean	171 ± 6	211 ± 12^{a}	250 ± 11^{b,c}
Range	120–210	90–300	180–330

Significant differences by analysis of variance and Student's *t*-test unpaired data: group I vs group II, ^{a}($P < 0.01$); group I vs group III, ^{b}($P < 0.001$); group II vs group III, ^{c}($P < 0.02$), ^{d}($P < 0.01$).

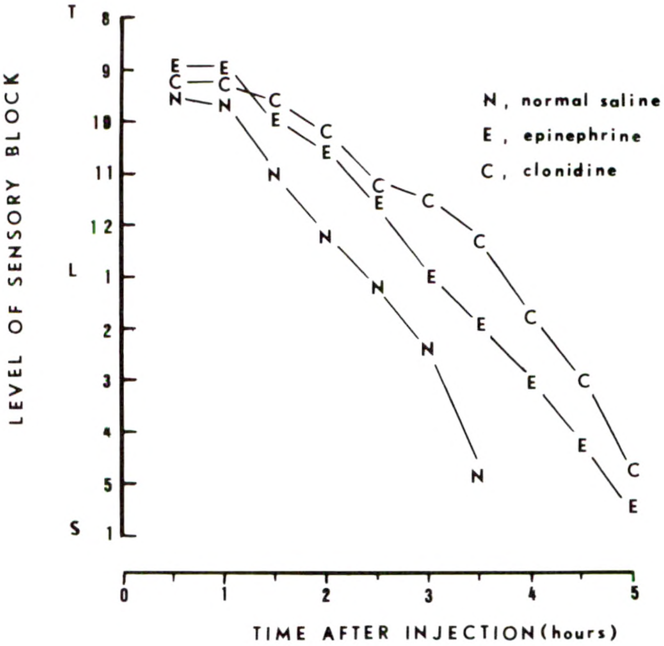

Figure 1. Mean levels and duration of sensory blockade after spinal anesthesia with 3 ml 0.5% bupivacaine plus 1 ml normal saline (N), or plus 0.2 mg epinephrine (E), or plus 0.15 mg clonidine (C).

Table 3. Characteristics of Spinal Motor Block in Different Groups

	Group I	Group II	Group III
Time to onset of total motor block: grade 3 (min)			
Mean	7.7 ± 0.6	6.8 ± 0.6	7.7 ± 0.8
Range	4–18	2–12	4–16
Duration of grade 3 motor block (min)			
Mean	152 ± 10	178 ± 12	210 ± 13^{b,c}
Range	90–240	75–270	120–240
Duration of grade 2 motor block (min)			
Mean	192 ± 11	217 ± 9	235 ± 14^{a}
Range	150–240	150–285	150–330
Duration of grade 1 motor block (min)			
Mean	222 ± 11	245 ± 9	264 ± 13^{a}
Range	150–300	150–300	180–345

Significant differences by analysis of variance and Student's *t*-test for unpaired data: group I vs group III, ^{a}($P < 0.02$), ^{b}($P < 0.001$); group II vs group III, ^{c}($P < 0.05$).

successful lumbar puncture. This patient was excluded from the analysis of the variables studied.

Sensory Blockade

Mean maximal levels of anesthesia (T10.7–T9.1) were similar in the three groups (Table 2). The rate of spread during onset was also similar.

Although the time to maximal levels varied greatly in all groups, ranging from 4 to 22 min, the mean values did not differ significantly (Table 2). The mean time from injection of the anesthetic to regression of the level of sensory anesthesia by two segments varied from 108 min to 171 min. There were significant differences in this variable between groups I and III ($P < 0.001$) and between groups II and III ($P < 0.01$). Compared with group I, the mean time for regression of the level of sensory anesthesia to L2 was significantly longer in group II (+40 min, +23.4%, $P < 0.01$) and in group III (+79 min, +46%, $P < 0.001$). Time to regression to L2 was also significantly longer (+39 min, +18.5%) with bupivacaine plus clonidine solution than with bupivacaine plus epinephrine solution ($P < 0.02$) (Fig. 1).

Motor Blockade

One patient in group III had incomplete motor blockade of the lower extremities. Except for this case, the time to onset of total motor block did not differ significantly among the three groups (Table 3). Significant differences in duration of grade 3 motor block were found between groups I and III (+58 min, +38%, $P < 0.001$) and II and III ($P < 0.05$). The duration of grade 2 and grade 1 motor blockade increased with administration of clonidine ($P < 0.02$).

Blood Pressure

Resting blood pressure did not differ significantly among the groups (Table 4). The administration of the bupivacaine with clonidine solution resulted in a decrease in systolic blood pressure of only 14.9% from the resting values. As shown in Table 4, the decrease

Table 4. Blood Pressure and Intravenous Fluid Administration

	Group I	Group II	Group III
Resting systolic blood pressure (mm Hg)			
Mean	143 ± 4	152 ± 4	140 ± 5
Range	104–160	110–180	100–180
Lowest level of systolic blood pressure (mm Hg)			
Mean	115 ± 6	119 ± 4	119 ± 4
Range	50–150	80–150	90–140
Mean % of resting values	−20.1 ± 3	−21.3 ± 2.3	−14.9 ± 1.5
Volume of lactated Ringer's solution given (ml·kg)			
Mean	18.1 ± 1.2	15.5 ± 1.2	17.2 ± 1.9
Range	8.1–30	6.7–22.2	6.8–28.6

in systolic blood pressure in group III was not significantly greater than it was in groups I and II. Six patients in group I, five in group II, and six in group III received ephedrine because of hypotension. No statistically significant difference was noticed among the groups in the amount of intravenous fluids given. For 12 hr after the block, the patients were kept supine in the surgical ward and no hypotension was encountered.

Discussion

The use of intrathecal vasoconstrictors is one of the main determinants of the duration of spinal anesthesia (10). Most (3,11) but not all (12) investigators have found that both epinephrine and phenylephrine produce significant prolongation of sensory and motor blockade during tetracaine spinal anesthesia. Controversy exists, however, with regard to the effect of these vasoconstrictors during lidocaine spinal anesthesia (13–15).

The present study showed that epinephrine prolongs significantly the duration of plain bupivacaine spinal anesthesia as measured by time of regression to the L2 level, without increasing the time for two-segment regression of the level of anesthesia. Plain bupivacaine was chosen because in hip surgery anesthesia is required at a specific level, and, when injected into the subarachnoid space in the horizontal position, isobaric solutions tend to remain in the injected area (10,16,17). This permits anesthetizing patients with hip fractures in their beds with the operative site uppermost. It has been also said that dextrose-free solutions of bupivacaine are associated with less risk of hypotension than are hyperbaric solutions (18,19), a matter of particular importance in elderly subjects. One criticism of the present study might be that all patients had the same dose of bupivacaine (15 mg in 4 ml). But in this study there were no significant differences in mean height among the groups, and there have been no controlled studies of the effect of patient height on distribution of spinal anesthetic solution (17). The dose of epinephrine we used, 0.2 mg, is the dosage used by Moore (3) with hyperbaric bupivacaine. There are no previous data on the effects of epinephrine on the duration of isobaric bupivacaine spinal anesthesia, but the present results are in agreement with studies of the effects of vasoconstrictors on hyperbaric bupivacaine spinal anesthesia, with Chambers et al. (20) finding no prolongation of two-segment regression time whereas Moore (3) showed that epinephrine 0.2 mg prolonged the mean duration of satisfactory anesthesia by an average of 48%.

The present study also indicates that, in isobaric bupivacaine spinal anesthesia in humans, clonidine increased significantly both the time for two-segment regression and the time for regression to L2, and did so more than epinephrine did. The dose of clonidine we used, 0.15 mg, was the same for all patients, but reported to mean weight (2.6 μg/kg) was relatively similar to that (3 μg/kg) used in epidural administration in humans (21). After intrathecal administration of high doses of clonidine in rats, no detectable lesions on the spinal cord and nerve roots were noted (22). Bedder et al., in an animal study (7), have shown that clonidine 0.150 mg when used as an adjunct to tetracaine spinal anesthesia is as effective as epinephrine 0.2 mg in prolonging motor blockade (+135% versus +116%), but significantly more effective (+107% versus +33%) in prolonging sensory blockade.

The mechanism of the prolongation of spinal blockade by vasoconstrictors is unknown, although it has been suggested that epinephrine may have a direct effect on neuronal transmission in the spinal cord (23). Direct application to the spinal cord of alpha-adrenergic agonist produces analgesia in both monkeys (4) and dogs (7).

Intrathecal clonidine has an analgetic effect (6,7,24). The mechanism of this action of intrathecal clonidine may be an activation of the postsynaptic α-2-adrenoceptors in spinal cord (25). This spinal activation has been invoked to explain the efficacity of clonidine in treatment of opiate withdrawal (26). Supraspinal effects of clonidine probably contribute in part to analgesia (27). The effect of intrathecal injection of this alpha-2-adrenoceptor agonist on spinal cord blood flow is unknown. However, local vasoconstriction in the spinal cord is not produced by epidural clonidine 3 μg/kg (28).

In conclusion, clonidine (0.15 mg) added to plain bupivacaine 0.5% spinal anesthesia is more effective than epinephrine (0.2 mg) in prolonging sensory and motor blockade.

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Epinephrine Enhances Analgesia Produced by Epidural Bupivacaine during Labor

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EISENACH JC, GRICE SC, DEWAN DM. Epinephrine enhances analgesia produced by epidural bupivacaine during labor. Anesth Analg 1987;66:447–51.

Reports on the analgesic and hemodynamic effects of epinephrine added to bupivacaine for epidural use in obstetrics are conflicting. In this study, healthy parturients received in a random manner either 10 ml of 0.25% bupivacaine (n = 50) or 10 ml of 0.25% bupivacaine with 1:300,000 epinephrine (n = 50) epidurally. Epinephrine enhanced the analgesia produced by bupivacaine: onset was hastened (5.8 ± 0.6 vs 8.7 ± 0.8 min, mean ± SEM, P < 0.05), duration prolonged (123 ± 7.0 vs 92 ± 5.0 min, P < 0.05), and the number of women requiring additional local anesthetic for analgesia decreased (9 vs 18, P < 0.05) compared to the group receiving plain bupivacaine. The incidence of hypotension did not differ between groups. Maternal heart rate increased only after injection of the epinephrine-containing solution. The authors conclude that epinephrine 1:300,000 modestly but statistically significantly improves the analgesic efficacy of epidurally administered 0.25% bupivacaine during labor.

Key Words: ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—epidural. ANESTHETICS, LOCAL—bupivacaine.

Epinephrine is added to local anesthetic solutions for epidural injection to prolong the duration of analgesia, to serve as a marker for accidental intravenous injection, and to decrease vascular absorption of local anesthetics from the epidural space, thus decreasing plasma levels and systemic toxicity of the local anesthetics. The effect of epinephrine on duration of analgesia may depend on the local anesthetic used. In parturients, epinephrine has been reported to prolong the duration of analgesia produced by 1.5% lidocaine (1). However, epinephrine has been reported both not to increase the duration of action of 0.5% bupivacaine (2,3) and to increase it by 120% (4). Because the use of epinephrine-containing local anesthetic solutions may have disadvantages in obstetric anesthesia (5,6), we reexamined the value of adding epinephrine to epidural bupivacaine.

Methods

The protocol was approved by the Clinical Research Practices Committee, and all patients gave informed consent. We studied 100 ASA 1 or 2 parturients with uncomplicated pregnancies, taking no medications, and with no history of cardiovascular disease. All women were in active labor and with cervical dilation <7 cm at the time they requested epidural analgesia. After subcutaneous infiltration with 1% lidocaine, we inserted a #16 Hythe needle into the epidural space at the L2–3, L3–4, or L4–5 interspace using the loss of resistance technique with air or a small amount (<3 ml) of saline. A single distal port Portex™ catheter was inserted no more than 3 cm beyond the tip of the needle. Patients were then positioned supine with left lateral tilt.

Before local anesthetic injection each woman was asked to rate her level of pain during uterine contractions on a 10 point scale (1 = no pain, 10 = worst pain ever experienced). Participants then received in a random manner 10 ml of either 0.25% bupivacaine plain or 0.25% bupivacaine with freshly added 1:300,000 epinephrine. The nurse and the patient were unaware of the assignment. We administered the local anesthetic solution in increments: 2 ml, followed in 5 min by 5 ml, followed in 2 min by 3 ml. If pain relief was inadequate 21 min after the 3 ml injection, the patient received an additional 5 ml of local anesthetic solution. If pain relief was inadequate 15 min after this injection, the patient was dropped from the study. The study ended at the time of the first reinforcing dose of local anesthetic, as requested by the nurse or

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Table 1. Patient and Labor Characteristics

Parameter	0.25% Bupivacaine plain (n = 50)	0.25% Bupivacaine with epinephrine (n = 50)
Age	26 ± 0.8	25 ± 0.9
Height (cm)	163 ± 3.3	163 ± 3.6
Weight (kg)	72 ± 2.0	74 ± 2.0
Cervical dilation (cm)	4.2 ± 0.2	4.3 ± 0.2
Nullipara/multipara	20/30	34/16[a]
Cesarean section	8	10
Duration of labor		
First stage (min)	224 ± 17	256 ± 23
Second stage (min)	95 ± 12	87 ± 10

Values expressed as mean ± SEM.
[a] $P < 0,05$ vs plain group.

Table 2. Analgesia after Epidural Injection

Parameter	0.25% Bupivacaine plain (n = 50)	0.25% Bupivacaine with epinephrine (n = 50)
Highest sensory dermatome		
Right	T-10 ± 0.3	T-10 ± 0.3
Left	T-10 ± 0.3	T-10 ± 0.3
Analgesia onset (min)	8.7 ± 0.8	5.8 ± 0.6[a]
Analgesia duration (min)		
All patients	92 ± 5	123 ± 7[a,b]
All patients given reinforcing dose[c]	89 ± 5	115 ± 7[a]
Patients requiring 15 ml	18	9[a]

Values expressed as mean ± SEM.
[a] $P < 0.05$ vs plain group. Refer to Methods for statistical tests employed.
[b] Includes patients who delivered prior to loss of analgesia from first dose. Analyzed by Kaplan–Meier survival function (7).
[c] n = 44 in plain group and 40 in epinephrine group.

patient, or, if no additional doses were required, at delivery.

Parturients assessed the adequacy of their pain relief on a 4 point scale (1 = none, 2 = a little, 3 = a lot, 4 = complete) every 3 min for 18 min, beginning 3 min after the 3 ml injection. At the end of this time, we determined the highest level of sensory analgesia to pin testing. We defined the onset of analgesia as time from the 3 ml injection until the patient reported a pain relief of 3 or 4. We defined duration of analgesia as time from the 3 ml injection until the patient requested additional analgesia.

We measured maternal blood pressure and heart rate with a Dinamap™ vital signs monitor before injection, every minute for 5 min after the 5 ml injection, then every 3 min for 18 min. We defined hypotension as a decrease in systolic blood pressure by 30% from the initial blood pressure measurement in the study or to a value below 100 mm Hg. We treated hypotension by increasing the rate of intravenous fluid administration and, if necessary, administering ephedrine. We also recorded maternal age, height, weight, parity, duration of first and second stage of delivery, mode of delivery, and 1 and 5 min Apgar scores.

Data are presented as means ± SEM. We used a Student's t-test for independent samples to compare the two groups for maternal demographic data, labor data, level of sensory analgesia, and, in patients receiving a redose, duration of analgesia. The level of sensory analgesia was also compared using the Kolmogorov–Smirnov frequency test. We used the Fisher–Yates exact probability test to determine the difference in incidence of noncontinuous labor and demographic data between groups. We eliminated from analysis blood pressure and heart rate data during uterine contractions and after ephedrine administration, and compared the remaining hemodynamic data between groups using a repeated measures two-way analysis of variance and, within groups, using a repeated measures one-way analysis of variance followed by Dunnett's multiple range test. Onset and duration of analgesia in all patients were compared by the Kaplan–Meier method (7) followed by the generalized Wilcoxon test. We considered $P < 0.05$ statistically significant.

Results

The groups differed in demographic and labor characteristics only in the greater number of nulliparous women in the epinephrine group (Table 1). All cesarean sections were performed because of cephalopelvic disproportion or failure to progress. All neonates were healthy, and no neonate had a 1 min Apgar score of less than 7.

The groups did not differ in baseline pain score (8.2 ± 0.2 in the plain group; 7.9 ± 0.3 in the epinephrine group). Although the groups did not differ in highest level of sensory analgesia achieved after injection of 10 ml of solution, the onset of pain relief was significantly hastened, the duration was significantly prolonged, and the number of women requiring additional local anesthetic was significantly decreased in patients given epinephrine (Table 2). Kaplan–Meier analysis, which includes patients "lost to follow-up" (those who delivered before loss of analgesia from the first injection), showed prolongation of analgesia in the epinephrine group (Fig. 1). Analgesia duration was prolonged in the epinephrine group regardless of whether the patients received 10 or 15 ml of solution (110 ± 7 vs 84 ± 5 min in those

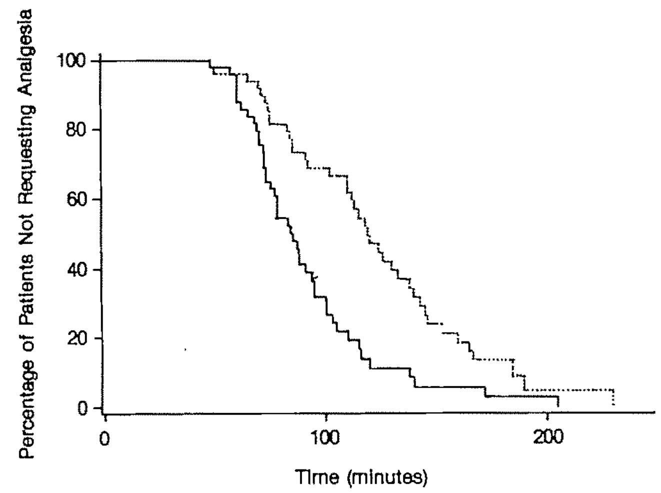

Figure 1. Duration of analgesia after epidural injection of 0.25% bupivacaine (—) and 0.25% bupivacaine with 1:300,000 epinephrine (···). Curves for each group were calculated by Kaplan–Meier analysis. The significance of the difference between groups is P = 0.0002 by the generalized Wilcoxon test.

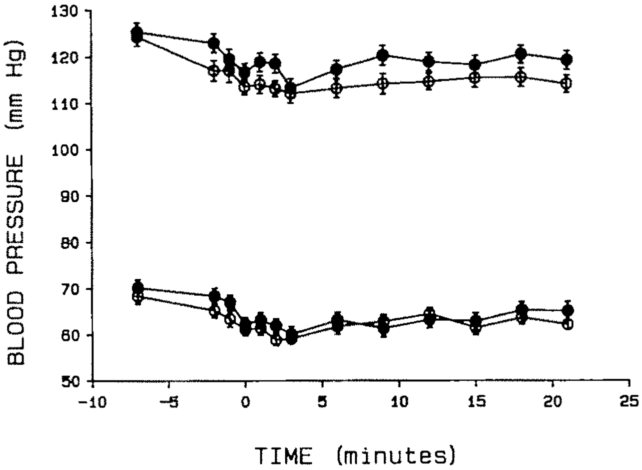

Figure 2. Blood pressure after epidural injection of 0.25% bupivacaine (○) or 0.25% bupivacaine with 1:300,000 epinephrine (●). The upper lines represent systolic, the lower lines diastolic blood pressure. Two milliliters of local anesthetic solution were injected epidurally at time = −7, 5 ml at time = −2, and 3 ml at time = 0 min. Each point represents the mean ± SEM of 42–50 patients. The groups do not differ by two-way analysis of variance.

receiving 10 ml; 138 ± 21 vs 97 ± 11 min in those receiving 15 ml; $P < 0.05$).

Blood pressure in the two groups did not differ, (Fig. 2) nor did incidence of hypotension (eight in the plain group, five in the epinephrine group) after epidural injection. Because the groups differed in baseline heart rate, we analyzed the data as absolute changes in heart rate from baseline. Heart rate increased after injection of epinephrine-containing bupivacaine, but not after plain bupivacaine (Fig. 3).

Discussion

Epinephrine alters the hemodynamic and analgesic effects of epidurally administered local anesthetics, partly by direct actions and partly by affecting local anesthetic disposition.

Hemodynamic Effects

The hemodynamic effects of epidurally administered epinephrine are consistent with peripheral β-, but not α-adrenoceptor activation. Alone, epidurally administered epinephrine (100 μg) decreases peripheral resistance and increases heart rate and cardiac output (8), probably because of peripheral β-adrenergic activation. Epinephrine may also decrease peripheral resistance by inhibiting preganglionic sympathetic neurons in the spinal cord (9). Combined with lidocaine to produce a T-5 level of sensory analgesia, epidurally administered epinephrine decreases blood pressure more than epidural lidocaine alone (8). However, we and others (4) observed no increased incidence of hypotension when epinephrine was added to bupivacaine for lumbar epidural analgesia in obstetrics.

Analgesic Effects

Epinephrine alone produces analgesia after epidural (10) and intrathecal (11) administration, probably by an α-adrenergic mechanism in the spinal cord dorsal horn (12). Dilute local anesthetic solutions and epinephrine may be additive in producing analgesia. We and others (3) noted a more rapid onset and greater intensity of analgesia produced by epidurally administered bupivacaine when epinephrine was added.

Epidurally administered epinephrine is thought to prolong analgesia by producing local vasoconstriction and limiting vascular absorption of local anesthetic. This effect may be diminished if the local anesthetic itself produces vasoconstriction. For example, intrathecally administered tetracaine increases spinal cord and dural blood flow (13), whereas bupivacaine decreases it (14). Intrathecal epinephrine inhibits the local increase in blood flow associated with tetracaine (13) and prolongs the duration of tetracaine (15), whereas epinephrine is ineffective in further decreasing local blood flow (14) or reliably prolonging the duration of bupivacaine (16). After epidural administration for analgesia in labor, epinephrine prolongs (by 80%) (1) the duration of 1.5% lidocaine, which by

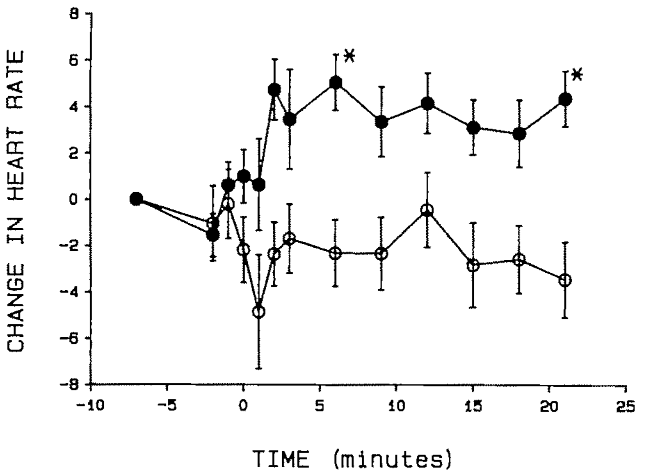

Figure 3. Effect of epidural injection of 0.25% bupivacaine (○) or 0.25% bupivacaine with 1:300,000 epinephrine (●) on change in heart rate from baseline levels. Two milliliters of local anesthetic solution were injected at time = −7, 5 ml at time = −2, and 3 ml at time = 0 min. Each point represents the mean ± SEM of 42–50 patients. The significance of the difference between groups is $P = 0.047$ by two-way analysis of variance. $^*P < 0.05$ vs time −7 min.

itself produces arteriolar vasodilatation (17), but has no (2,3) or a smaller (34% prolongation, this report) effect when added to bupivacaine (which also by itself produces arteriolar vasoconstriction) (18).

In contrast to these findings, Abboud et al. (4) reported a marked prolongation of analgesia (by 120%) when epinephrine was added to bupivacaine for epidural analgesia in laboring parturients. Differences between that study and the present one that could account for this discrepancy include:

1. Drug administration and analgesia duration endpoint determination (not stated by Abboud et al. (4) vs random, blinded in this study). A random, blinded design diminishes the likelihood of investigator bias influencing the outcome of the study, particularly when subjective parameters (pain measurement) are measured. In this study, duration of analgesia, as defined by time to first reinforcing dose of local anesthetic, was determined in all cases by a person unaware of the drug assignment. Using a random, blinded design, others (2,3) have found no increase in duration of analgesia produced by epinephrine.
2. Statistical design (*t*-tests by Abboud et al. (4) vs Kaplan-Meier analysis in this study). Although not stated by Abboud et al. (4) some patients in their study may have delivered before loss of analgesia from the epidural injection. Because patients may be "lost to follow-up" in unequal numbers between groups and at variable times into the study, ignoring them may affect the validity of the conclusions reached. The Kaplan–Meier analysis avoids this problem by including all patients.
3. Epinephrine dose (26 μg (average) by Abboud et al. (4) vs 37.5–56.2 μg in this study). If epinephrine prolongs analgesia by producing analgesia directly or by local vasoconstriction, one would expect a larger, not smaller effect with the larger dose used in this study.
4. Bupivacaine concentration (0.5% by Abboud et al. (4) vs 0.25% in this study). In the only comparison of bupivacaine concentrations, Covino and Scott (3) reported a greater effect of epinephrine added to 0.25% bupivacaine (31% prolongation—similar to the 34% prolongation we observed) than to 0.5% bupivacaine (none).
5. Length of study (repeated doses by Abboud et al. (4) vs first dose only in this study). Although the cumulative effect of epinephrine-containing epidural injections of local anesthetic could enhance the effect on duration and explain the greater effect reported by Abboud et al. (4), no such cumulative effect was observed by Reynolds and Taylor (2).

Other reasons for including epinephrine in bupivacaine solutions for epidural analgesia in obstetrics are to decrease fetal exposure to bupivacaine, which produces behavioral effects lasting weeks in the newborn (19), and to produce early warning of intravascular injection of local anesthetic solutions (20) and cardiac support in the event that blood levels of local anesthetics become high enough to induce cardiotoxicity (21). However, these benefits have not been demonstrated in controlled clinical studies. Maternal plasma bupivacaine concentrations after epidural injection are minimally decreased by epinephrine, and the fetal: maternal plasma bupivacaine concentration ratio increases (2). Intravenous epinephrine, in a dose that reduces uterine blood flow by 45% in ewes (5) produces hemodynamic changes in parturients subtle enough to require sophisticated monitoring to detect (22).

In summary, we observed a small but statistically significant prolongation (31 min) in the duration of analgesia produced by addition of epinephrine 1: 300,000 to epidurally administered 0.25% bupivacaine. The discrepancy between these findings and those reported by Abboud et al. (4) may be due to differences in study design and statistical evaluation. Prolongation of analgesia by epinephrine must be weighed against potential complications (decreased uterine blood flow, prolongation of labor, accidental unrecognized intravenous injection) that may occur with use of epinephrine-containing local anesthetics in obstetrics.

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Prior Carotid Surgery Does Not Affect the Reliability of Landmarks for Location of the Internal Jugular Vein

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HORROW JC, METZ S, THICKMAN D, FREDERIC MW. Prior carotid surgery does not affect the reliability of landmarks for location of the internal jugular vein. Anesth Analg 1987;66:452–6.

Twenty-one volunteer subjects who had undergone prior carotid endarterectomy (CEA) agreed to an ultrasound study of the neck. The transducer was held as one would hold a cannulating needle and ultrasound images were obtained of the great vessels in the neck. Each of two cannulating techniques was simulated on each side of every patient's neck. Photographs of the ultrasound images were analyzed to score "hit" or "miss" for the internal jugular vein (IJV) and the carotid artery (CA), and to measure both the angle between these vessels and the distance from the skin to the IJV. In 11 subjects, the effect of a Valsalva maneuver on IJV width was also determined. Owing to bilateral CEA in 9 of the 21 subjects, there were 12 studies of nonsurgical sides (NSS) and 30 studies of surgical sides (SS). SS and NSS hit frequencies were statistically indistinguishable both for the IJV and the CA. In no photograph did the IJV lie medial to the CA. A Valsalva maneuver did not change IJV width on either the SS or the NSS. These data show that prior CEA does not affect the location of the IJV. Tissue alterations or adhesions may render actual IJV cannulation more difficult or risky. The data suggest but do not prove that prior CEA may not increase the incidence of CA puncture under clinical conditions.

Key Words: VEINS, INTERNAL JUGULAR—cannulation. MEASUREMENT TECHNIQUES—ultrasound. MONITORING—jugular cannulation. SURGERY—carotid endarterectomy.

Cannulation of the internal jugular vein (IJV) is commonly performed to establish central venous access. Because carotid endarterectomy (CEA) is presumed to alter the relation between the IJV and surface landmarks, prior CEA and other neck surgery are considered by many (1–3) to be at least relative contraindications to IJV cannulation. Clinicians who find no IJV site suitable for cannulation by this criterion may be compelled to select another site for central venous access or do without central venous access altogether. Either of these options may have adverse effects on patient care.

The reliability of landmarks for IJV cannulation after CEA has not been tested clinically. Any investigation of landmark reliability using cannulating needles would cause the experimental subjects unacceptable discomfort and risk. Ultrasound (US), a noninvasive procedure associated with no known complications, has been utilized to study the IJV (4–6). We employed US to investigate the neck anatomy at both surgical sites (SS) and nonsurgical sites (NSS) in 21 subjects with prior CEA.

This investigation sought to answer several questions: 1) Does prior CEA alter the reliability of landmarks commonly used to identify the IJV? 2) Does the anatomic relation between the IJV and CA on the SS differ from that on the NSS? 3) Is the depth of the IJV from the skin surface different after CEA? Midway through the study, we observed that the Valsalva maneuver did not seem to increase the size of the US image of the IJV on the SS. Therefore, in the last 11 patients, we compared the change in IJV width on the SS with that on the NSS to determine whether prior CEA limits the IJV distension that normally occurs with the Valsalva maneuver.

Methods

This study was approved by our institutional review board. Sixty-four patients seen by a single neurologist (MWF) and who had recent CEA performed on one

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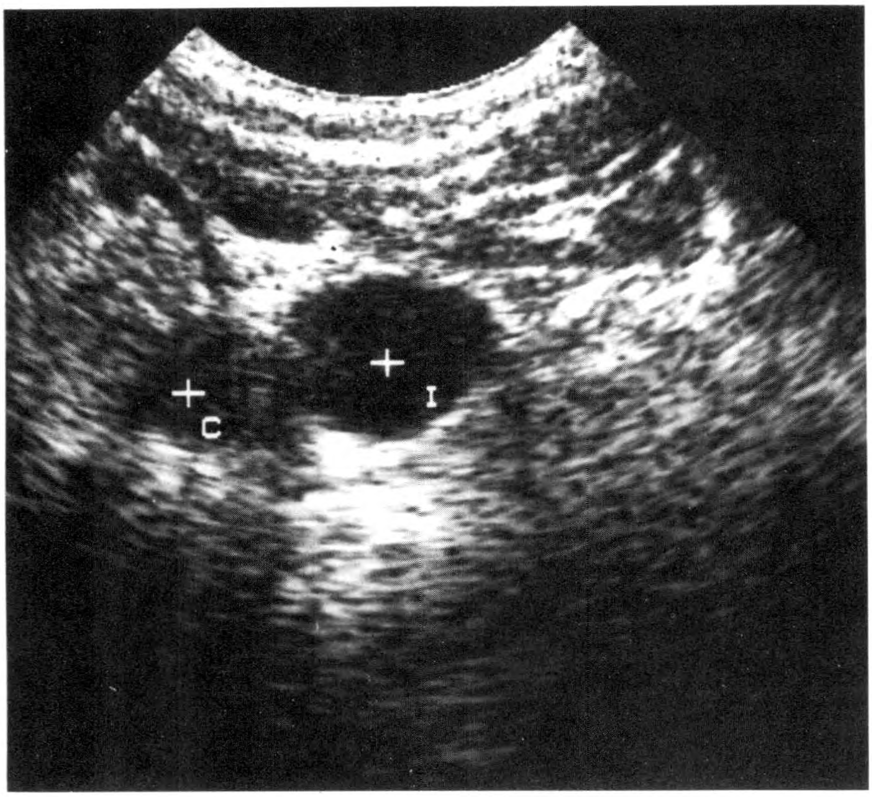

Figure 1. Ultrasound image of the right neck using the apical technique viewed from the patient's head (left side of image is medial). The internal jugular vein (**I**) lies in the midline of the image and is scored as "hit." The slightly smaller carotid artery (**C**) is found medial and posterior to the IJV and is scored as "miss." Crosshairs (+) are placed at the estimated vessel centers.

or both sides were asked by letter to participate in the study. There were 34 responses: 9 patients had died since their last visit; 4 declined participation; and 21 patients (33%) enrolled in and completed the study. Age, gender, and past surgical history were recorded for each participant.

Two commonly used techniques were selected as representative of two families of approaches to the IJV: the apical approach and the anterior approach (7). The chosen apical technique (8) employs as a landmark the apex of the triangle formed by the heads of the sternocleidomastoid muscle and the clavicle. For the chosen anterior approach (9), the carotid pulsation, independent of surface anatomy, serves as a landmark.

Each patient lay supine with minimal head down tilt. The right side was always investigated first. The subject was positioned according to the instructions for the apical approach (8). The US transducer was placed on the neck and directed like a needle according to the directions for that technique. Care was taken to avoid excessive pressure while simultaneously achieving sufficient contact for imaging. One investigator (DT) viewed the US image and identified and labeled arterial and venous structures according to their anatomic orientations, pulsation patterns, and when necessary, by Doppler wave patterns. If either vessel was not visualized, this was noted. A photograph of the real-time image was obtained during normal respirations. Figure 1 shows a representative photograph. This procedure was repeated for the anterior technique (9) on the right side. The patient was then repositioned and the two procedures repeated on the left side.

In 11 of the 21 patients, the effect of the Valsalva maneuver on IJV size was evaluated. On both the right and left sides, after obtaining the sonogram for the anterior technique, we instructed the patient to inhale deeply, hold his or her breath, and "bear down as if trying to have a bowel movement," while an additional anterior technique image was obtained.

US images were obtained with an ATL (Bellevue, WA) real-time ultrasound scanner with mechanical sector transducers of 3.5–10 MHz. The focal zone ranged from 0.6 to 8.0 cm. The transducer selection and levels of power, near gain, far gain, and slope were optimized for each patient. Standard water-soluble gel was used as the sole coupling agent. Distance from the skin to IJV was measured from the US display screen using digital calipers with a deviation of 2%. Photographs were taken from a real-time image in the transverse plane angulated along the path of a presumed locating needle.

Each ultrasound image provided the following data: the intersection of the axis of the transducer with the image of the IJV, scored as "hit" or "miss"; similar

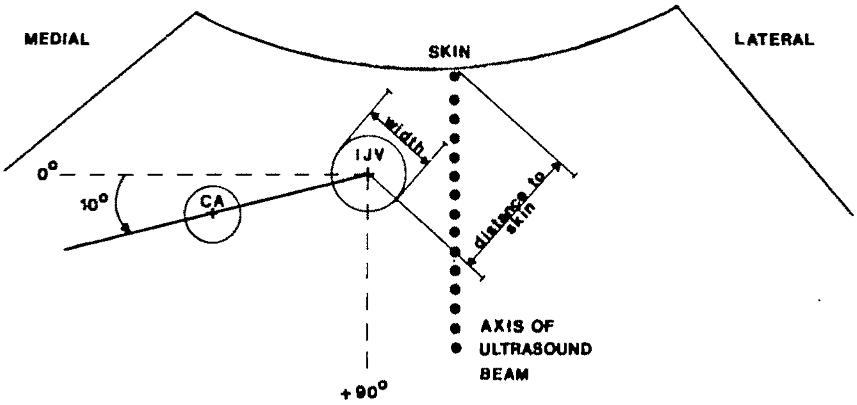

Figure 2. Line drawing showing measurements of a typical photograph on the right side. In contrast to Figure 1, in this schematic diagram neither the IJV nor the CA would be scored as "hit." The axis of the transducer, which indicates the presumed path of a cannulating needle, is represented by a dotted line. The skin to IJV distance and IJV width are each indicated by a double-headed arrow. See text for measurement specifications. The angle between IJV and CA is denoted by the curved arrow. The 0° and +90° axes for angle measurement are indicated by broken lines.

scoring for the intersection of the axis of the transducer with the image of the CA; the distance along a needle's path from the skin to the center of the IJV image; and the angle between the IJV and the CA. The angle to the center of the CA was measured by placing the origin of a protractor on the center of the IJV image using 0° as medial and +90° as posterior (deep). The width of the IJV was measured in those images used to evaluate the effect of the Valsalva maneuver. IJV width was obtained along a line perpendicular to the path of a needle oriented to achieve successful cannulation even if that path were lateral or medial to the transducer axis. Figure 2 is an example of how these measurements were performed.

Frequency data were analyzed by χ^2 contingency tables. Continuous variables were analyzed by paired or unpaired Student's t-tests. Significance was defined as $P < 0.05$.

Results

Thirteen men and eight women, aged 54–85 yr (mean 68) completed the study. These patients had undergone between zero and four other vascular surgical procedures (mean 0.6). No patient had had other surgery on the neck or had received radiation to the neck. The time elapsed between CEA and this study ranged from 6 months to 10 yr (mean 3yr). Four patients had had surgery on the right side, eight on the left, and nine on both sides. In one patient, the left CA was not palpable, preventing study of the anterior technique on that side. Thus there are 12 studies of both apical and anterior techniques on NSS, and 30 studies of the apical technique and 29 studies of the anterior technique on SS.

The IJV was visualized in every view; the CA was visualized in 72 of 83 views. Table 1 displays the hit frequency data for the two techniques on the SS and the NSS. There were no statistical differences between the SS and NSS hit frequencies for either technique for either the IJV or the CA.

The distance from the skin to the center of the IJV was 2.15 ± 0.53 cm (mean ± SD). Distance from skin to IJV did not vary with technique or from SS to NSS. The angle between the CA and IJV was +9 ± 24° (mean ± SD, $n = 49$) on the SS and +20 ± 21° ($n = 20$) on the NSS (P = NS, unpaired t-test). In no photograph did the IJV lay medial to the CA (angle >90° or <−90°).

The effect of the Valsalva maneuver on IJV width is demonstrated in Table 2. Although the mean values of IJV width during the Valsalva maneuver appear numerically greater on both the NSS (0.38 ± 0.40) and the SS (0.21 ± 0.18), only the SS data achieve statistical significance. The increase in IJV width on the SS is not statistically different from that on the NSS (unpaired t-test, $P > 0.2$).

Discussion

Standard anesthesia texts state that prior surgical procedures on the neck are relative contraindications to IJV cannulation at those sites (1–3). Though these recommendations are unreferenced, one concern may be that fibrosis, adhesions, scar formation, and surgical manipulation itself render surface landmarks unreliable as guides to location of the deeper structures, including the IJV.

Two common surface landmarks used in locating the IJV are the apex of the sternocleidomastoid muscle and the carotid pulse. Our study determined that after CEA, these landmarks retain their reliability in locating the IJV and in directing attention lateral to the CA. Additionally, no difference in reliability was demonstrated between the apical and the anterior landmarks, both at nonoperated and operated sites.

Table 1. Hit Frequency Data[a]

	IJV HIT	IJV MISS	% IJV HIT	CA HIT	CA MISS	% CA HIT	CA NONVIZ
Apical-SS	24	6	80%	3	24	11%	3
Apical-NSS	9	3	75%	3	7	30%	2
Anterior-SS	23	6	79%	2	20	9%	7
Anterior-NSS	8	4	67%	2	8	20%	2

Abbreviations used: IJV, internal jugular vein; CA, carotid artery; SS, surgical side; NSS, non-surgical side; NONVIZ, not visualized.
P = NS by χ^2 for Apical vs Anterior and for SS vs NSS for both IJV data and CA data.
[a]Entries are numbers of subjects except where indicated.

Table 2. IJV widths[a]

	Without Valsalva	With Valsalva	Increase	*P* value
SS (n = 14)	1.1 ± 0.49	1.3 ± 0.47	0.21 ± 0.18	<0.001
NSS (n = 6)	1.0 ± 0.40	1.4 ± 0.52	0.38 ± 0.40	0.07
BOTH (n = 20)	1.1 ± 0.46	1.4 ± 0.47	0.26 ± 0.26	<0.001

Increase refers to the paired difference of IJV width during Valsalva minus the IJV width without Valsalva's maneuver. *P* values are for the null hypothesis that the increase is different from zero.
[a]Entries are cm (mean ± SD).

This latter result agrees with a previous ultrasound investigation in which 15 different techniques were all equivalent with regard to IJV localization (4).

The overall IJV location rate of 77% in our current study compares favorably with the rate of 52% found previously (4). CA "hit" frequency data are similar: 14% in this study, 20% in the previous one. Thus our current study shows slightly higher IJV and slightly lower CA hit rates. Improvement with time of the investigators' skill cannot explain this difference because both the ultrasound equipment and the ultrasonographer were different. Technique selection may account for the seemingly superior results in our current study.

The 14% CA hit rate is high compared with those reported in original descriptions of the techniques (range 0–4%). As explained in the previous US study (4), this discrepancy may be accounted for by both underreporting of CA punctures in the original papers (as when only a small-gauge finder needle discovers the CA) and overreporting of CA punctures in the US studies (as when both CA and IJV align along the transducer axis). In the latter case, a needle slowly advanced along that path would discover the more superficially placed IJV first and never reach the CA, whereas the US studies score hit for both IJV and CA.

In young healthy volunteers (4), the IJV was found lateral and anterior to the CA (angle +21 ± 21°). The current data substantiate this relation in elderly patients (+20 ± 21° on the NSS). Furthermore, this relation was not altered by CEA, the IJV remaining slightly anterior to the CA in most cases and lateral to the CA in all cases.

Initial observations suggested that surgical adhesions might be preventing expansion of the IJV on the SS during the Valsalva maneuver. The results show the opposite effect: the Valsalva maneuver increased IJV width significantly on the SS but not the NSS. The previous study (4) in young, healthy volunteers revealed that IJV width was larger with breathholding than without. Thus lack of statistical significance for increased IJV width on the NSS is surprising, and most likely results from too few observations in this group (n = 6) rather than from a true distinction from the SS data. Perhaps for a similar reason, we could not demonstrate that the Valsalva maneuver widened the IJV more on the NSS than the SS. Power analysis predicts that over 30 patients in each group would be required to demonstrate a significant difference at the P = 0.05 level. In any event, neither study suggests an increased success in locating the IJV during breathholding, although this maneuver may still assist in preventing air embolism during cannulation.

Several factors prevented our study from precisely reproducing clinical circumstances. Unlike a needle tip that affords complete visualization of the puncture site, the transducer obscures about 1 cm^2 of skin underneath it. Thus the bulkiness of the transducer impairs the accuracy of its placement. Likewise, pressure on the skin from the transducer might have distorted the underlying anatomy unlike the distortion of skin-tenting from a probing needle. Skin toughness and subcutaneous fibrous adhesions can theoretically lead a probing needle astray. Thus a clear path as shown by US to the IJV, or CA for that matter, might not be the one traversed by a needle identically aimed. Of course, real-time US guidance of percutaneous procedures is well-established clinically and has been used for IJV location (6,10). Nevertheless, our study assessed neither ease of needle placement nor ease of cannulation.

More important, patients who have undergone CEA may have residual or recurrent atheromatous carotid arterial disease. Fear of dislodging plaque with subsequent stroke leads some clinicians to avoid manipulation of the neck in every patient with carotid artery disease, irrespective of prior CEA on that side. Finally, patients with CEA performed within 6 months of this investigation were excluded. It is possible, but unlikely, that surface landmarks are less reliable at sites of more recent CEA.

Because the axis of the US transducer intersected the IJV in only 77% of the images, but intersected the CA in 14%, we recommend that a small gauge finder needle be used in all cases to confirm the location of the IJV before cannulation is attempted.

In conclusion, these data in elderly patients show that the relation between the IJV and CA is similar to that in younger patients and is not altered by CEA performed at least 6 months before. Furthermore, the location of the IJV and the reliability of landmarks used to locate the IJV are not altered by prior CEA. The data suggest but do not prove that under clinical conditions, the incidence of CA needle puncture might not be altered by prior CEA.

The authors are grateful to the patients who participated in this study and to Jeremy R. Jaffe, who provided artwork for Figure 2.

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Clinical Reports

Decreasing Airflow Resistance during Infant and Pediatric Bronchoscopy

Andrew M. Woods, MD, and Thomas J. Gal, MD

Rigid bronchoscopy in infants and small children is fraught with problems of inadequate ventilation and gas exchange, due in part to compromise of the lumen of a small-caliber bronchoscope by insertion of a telescope (1). The standard Storz-Hopkins pediatric telescope has an outer diameter of 4.0 mm whereas the smallest Storz 30-cm-bronchoscope has an inner diameter of 4.9 mm. The size of this bronchoscope, designated by the manufacturer (nominal size), is actually 3.5 (Table 1). Thus the 4.0-mm telescope occupies about two-thirds of the cross-sectional area of the 3.5 bronchoscope lumen and impedes airflow (2). This bronchoscope is the size usually required for children under 3 yr of age, the group in which the largest proportion of anesthetics is administered for pediatric bronchoscopies (3).

A smaller telescope (Hopkins 27020 A) that is currently available, although marketed for use with the Storz optical forceps, fits all Storz 30-cm-long bronchoscopes. The diameter of this telescope (2.8 mm) would present much less resistance to airflow, but there are no actual measurements to prove this or to indicate how much the resistance is decreased. This study was performed to compare this smaller diameter telescope with the standard 4.0-mm telescope principally in terms of airflow resistance, but brightness and image resolution were compared as well.

Methods

The pressure gradients across a range of Storz pediatric bronchoscopes were measured with differential pressure transducers (Validyne MP-45, range 0 ± 5 cm H_2O and 0 ± 50 cm H_2O). Pressures were sampled at the proximal side arm and at the distal end of the bronchoscopes. Measurements were made during oxygen flows of 3 and 6 L/min, which are in the range for spontaneously breathing infants. The oxygen flow was delivered by an Ohio 2000 anesthesia machine with the accuracy checked by measuring volume per unit time delivered to an electronic spirometer (Ohio model 840). Use of steady flows to determine pressure gradients in this experiment is relevant to normal physiology since the fluid dynamic characteristics of flow during both normal breathing and mechanical ventilation can be considered quasi-steady (4).

The three bronchoscope sheaths utilized have nominal sizes of 3.5, 4.0, and 6.0 mm, but the actual internal diameters are 4.9, 5.9, and 7.4 mm, respectively (Table 1). Resistance was calculated by dividing the pressure drop (cm H_2O) by the flow rate (L/sec). The following configurations were studied for each of the three bronchoscopes: (1) no telescope (NT), (2) a standard 4-mm by 30-cm telescope ($T_{4.0}$), and (3) a 2.8-mm by 30-cm telescope ($T_{2.8}$).

Results

With no telescope in place, the airflow resistances were minimal regardless of the size of the bronchoscope (Fig. 1). Resistance through the 6.0 bronchoscope was also minimal with either telescope.

With the 4.0 bronchoscope, the standard 4.0-mm telescope ($T_{4.0}$) produced flow resistances only slightly greater than the normal range of upper airway resistance (R_{uaw}) for infants (5), indicated by the horizontal striped bar (Fig. 1). Substitution of the smaller 2.8-mm telescope ($T_{2.8}$) for $T_{4.0}$ decreased this resistance by 40% at flow rates of both 3 and 6 L/min.

Use of $T_{4.0}$ in the 3.5 bronchoscope was associated with marked increases in airflow resistance to ap-

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Table 1. Dimensions of Rigid Bronchoscopes

Nominal size (mm)	Internal diameter[a] (mm)	External diameter[a] (mm)
2.5	3.2	4.0
3.0	4.2	5.0
3.5	4.9	5.7
4.0	5.9	6.7
5.0	7.0	7.8
6.0	7.4	8.2

[a] Measured with caliper and verified by Karl Storz Endoscopy-America, Inc.

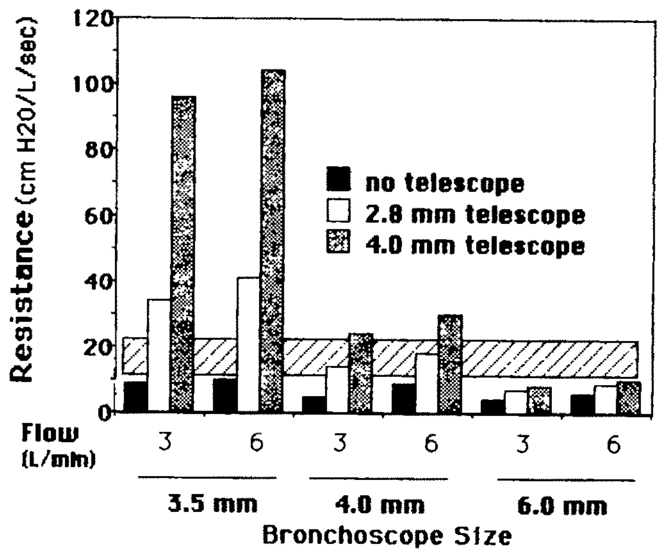

Figure 1. Resistance to airflow through pediatric bronchoscopes with and without telescopes in place. Horizontal striped bar indicates range of normal infant upper airway resistance (5).

Table 2. Resistance (cm $H_2O \cdot L^{-1} \cdot sec^{-1}$) of Neonatal Endotracheal Tubes

Internal diameter (mm)	Flow	
	3 L/min	6 L/min
2.5	78	88
3.0	40	48
3.5	26	30

proximately five times the upper limit of normal R_{uaw}. Replacing $T_{4.0}$ with $T_{2.8}$ reduced flow resistances to levels approximately 1.5 times the normal R_{uaw} at 3 L/min and twice the normal R_{uaw} at 6 L/min. Thus, at both flow rates studied, $T_{4.0}$ produced more than 2.5 times the resistance of $T_{2.8}$ when used in the 3.5 bronchoscope.

For purposes of comparison, resistances to flow through several sizes of pediatric endotracheal tubes (Portex 2.5, 3.0, and 3.5 mm internal diameter, with connector) were also measured (Table 2). When we breathed quietly through these, we felt that the 3.5 bronchoscope with $T_{4.0}$ in place was similar to breathing through a 2.5-mm endotracheal tube. Replacing $T_{4.0}$ with the smaller $T_{2.8}$ allowed for easier breathing through the bronchoscope, and subjectively was similar to breathing through a 3.5-mm endotracheal tube. These subjective impressions correlate well with the measured resistances to flow.

Measurements with a Luna-Pro light meter 1.5 cm from the distal tips of the telescopes showed that the 4.0-mm scope was one f-stop brighter, corresponding to a light intensity nearly twice that of the 2.8-mm scope. Photographs taken through the two telescopes (Fig. 2) illustrate the larger image size and finer detail achieved with the 4.0 telescope. The image with the smaller $T_{2.8}$ appears quite distinct, however.

Discussion

Resistance to airflow imposed by the 3.5 bronchoscope with the standard telescope ($T_{4.0}$) is approximately five times the normal upper airway resistance of infants (Fig. 1). Healthy, spontaneously breathing infants should be able to maintain adequate gas exchange for short periods despite this increased resistance, even under general anesthesia (6). However, this high resistance poses a particular hazard to sick infants, and especially those in whom paralysis is utilized as part of an anesthetic technique. Infants with lung disease resulting in low pulmonary compliance may not be able to tolerate the increased work of breathing imposed by the increased upper airway resistance. In paralyzed infants, the passive elastic recoil of the lungs and chest wall, which provides the driving pressure for deflation of the lungs, is insufficient to overcome the expiratory resistance of the bronchoscope/telescope apparatus within the short time period allotted for exhalation (7). Staircasing of lung volumes is likely, resulting in both hypercarbia and increased intrathoracic pressure with subsequent impairment of cardiac output and risk of barotrauma.

This high resistance to airflow can be significantly reduced by use of the smaller 2.8-mm telescope in the 3.5 bronchoscope. The pressure gradients associated with 3 L/min flow (1.6 cm H_2O) and 6 L/min flow (4 cm H_2O) are well below the normal recoil pressures of infants and thus should allow more adequate lung deflation. Lower resistances can also be obtained by using a larger bronchoscope with the standard 4.0-mm telescope. However, to allow use of a 4.0 bronchoscope, the infant's airway must be large enough to accommodate a 5.0 endotracheal tube, since the outer diameter of this tube (6.9 mm) is approximately

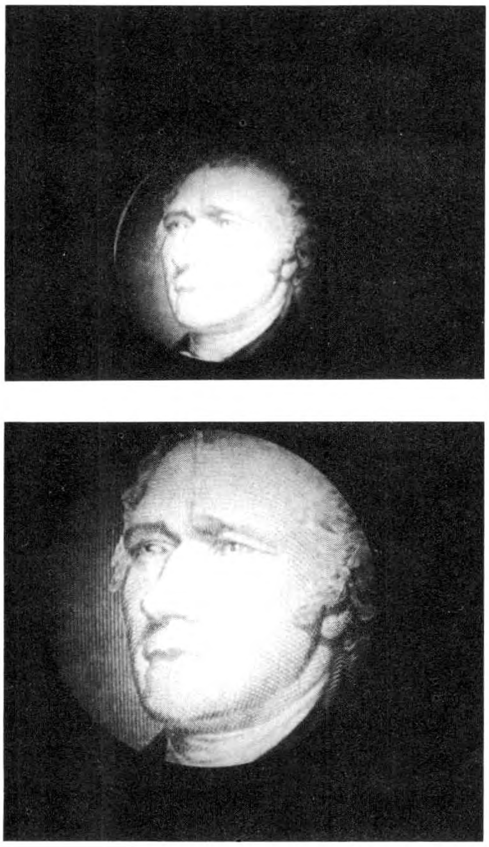

Figure 2. Photographs taken through the Storz-Hopkins 2.8-mm telescope (top) and the 4.0-mm telescope (bottom).

the same as that of the 4.0 bronchoscope (6.7 mm). This size of airway is usually found in children over the age of 3 yr. For pediatric patients younger than this, it would appear that the 2.8-mm telescope provides the best solution to the problem of high airway resistance.

If the larger telescope ($T_{4.0}$) is used with the 3.5 bronchoscope, the anesthesiologist must be aware of the increased risk of adverse cardiopulmonary effects. Frequent, periodic withdrawal of the telescope from the bronchoscope is necessary to reestablish a low-resistance airway and reduce the risk of air trapping. Such withdrawal of the telescope is particularly critical with the smaller sized (2.5-mm and 3.0-mm) neonatal bronchoscopes.

Our measurements, however, suggest that this high flow resistance is not a problem when the $T_{2.8}$ is utilized instead of the standard $T_{4.0}$ with the pediatric sized (3.5) bronchoscope. While the trade-off in optical quality with $T_{2.8}$ may be significant for endoscopic photography, it does not appear to be so for most clinical applications.

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Bacteremia as a Complication of Nasotracheal Intubation

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Instrumentation of the upper airway has been shown to be associated with bacteremia (1–3). In addition to endoscopy and suctioning, tracheal intubation has been implicated in bacteremic episodes. Positive blood cultures have been reported with both orotracheal (OT) and nasotracheal (NT) routes of intubation (4,5). In one study the risk of bacteremia was, albeit small, greater with OT than with NT intubation (4), whereas in another study the reverse was true.

Nasotracheal intubation is frequently necessary during dental and orofacial surgery. It is also a practical means of airway control in conscious patients with respiratory insufficiency, in intensive care patients for long-term maintenance of the airway, and in surgical patients who are difficult to intubate by the OT route. Not infrequently patients requiring NT intubation are immunocompromised or have valvular heart lesions and thus are susceptible to complications associated with even transient bacteremia, including subacute bacterial endocarditis. The present prospective study was undertaken to determine the incidence of bacteremia associated with NT intubation.

Materials and Methods

The study protocol was approved by the New York Hospital Cornell Medical Center Committee on Human Rights and informed consent was obtained from all patients. Fifty-four ASA physical status 1 or 2 patients aged 14–88 scheduled for dental or maxillofacial surgery were studied. To be included patients must have met the following criteria: 1) no preexisting nasopharyngeal pathology; 2) NT intubation was necessary because of the type of surgery; 3) no evidence of immunocompromise; 4) no known cardiac defects; 5) no recent procedures (e.g. dentistry, insertion of arch bars); 6) antibiotics had not been administered within 72 hr; 7) no evidence of preexisting infectious disease; and 8) the absence of nasogastric tubes, jaw wires, etc. in the upper airway.

Blood for culturing was obtained in all patients before intubation and again 2 and 10 min after NT tube placement. During this 10-min interval, no other manipulations were made in the airway of the patients. In 27 of the 54 patients, vasoconstriction of the nasal mucosa was produced by the topical application of a 0.1% xylometazoline (Neosynephrine II®) solution. Patients receiving vasoconstriction were allocated randomly. In all cases, the tube was lubricated with either saline or a water soluble lubricant. Trauma associated with the intubation was graded as follows: I, atraumatic (a bloodless, easy NT intubation); II, slightly traumatic (the presence of blood tinged sputum with suctioning following intubation); III, frankly traumatic (blood pooling in the oropharynx or the nose).

Blood for culturing was obtained from an antecubital vein in the arm opposite to that with the intravenous infusion. Twelve milliliters of blood per culture were drawn by venipuncture after sterile preparation of the site with povidone iodine. Each blood culture consisted of three bottles containing 70–90 ml of the following media: 1) beef-heart infusion (BHI) broth prepared at the New York Hospital; 2) thiol broth (Difco); and 3) tryptic-soy broth (TSB) (Scott). All blood cultures were routinely passed to chocolate agar from TSB and BHI after incubation for 24 hr and from BHI after incubation for 4 days. The microbiology laboratory at the New York Hospital performed all culture processing and identification of organisms.

Results

Of the 54 patients studied, three (5.5%) had bacteremia after NT intubation. Cultures were negative in all patients before intubation. The three patients with positive blood cultures were from group I (atraumatic intubations). There were no positive cultures after intubation in patients in whom intubation was traumatic even though slight or gross trauma occurred in 39% of the patients (21 of 54). Two of the three

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Table 1. Results of Blood Cultures after Nasotracheal Intubation

Patient number	Vasoconstrictor use	Trauma scale (number of patients)	Bacteremia
1–27	All	I (15)	2 (*S. mitior, H. Influenza*)
		II (9)	0
		III (3)	0
28–54	None	I (18)	1 *S. milleri*
		II (8)	0
		III (1)	0

patients with positive cultures had had the topical vasoconstrictor used. The remaining patient had not.

The microorganisms isolated were from the *Streptococcus viridans* group in two patients (*S. mitior* and *S. milleri*) and *Hemophilus* influenza in the other. In no patient was a skin contaminant such as *Staphylococcus epidermidis* found in the blood cultures. One patient had bacteremia only in the 2-min blood sample, one had bacteremia only in the 10-min sample, and one patient had bacteremia in both the 2- and 10-min samples.

Discussion

The risk of bacteremia associated with instrumentation of the upper airway depends on the nature of instrumentation, the presence or absence of underlying diseases and the methods used for determining the presence or absence of bacteremia. Burman (6) reported, for example, the highest potential for bacteremia by demonstrating bacteremia in 33% of febrile patients undergoing rigid bronchoscopy. In contrast, Smith et al. (7) found no bacteremia in afebrile patients undergoing flexible bronchoscopy.

Previous studies of the incidence of bacteremia associated with NT intubation are similarly conflicting. Baltch et al. (8) found bacteremia in 33% (10 of 30) of patients after NT intubation for dental surgery. Ninety percent of all the patients in their study had severe periodontitis or periapical abscess formation. Similarly, Berry et al. (5) found a 12% (4 of 34) incidence of bacteremia after NT intubation in pediatric patients undergoing dental restorative procedures, though no blood samples for culturing were obtained prior to intubation. At the other extreme is the study by Gerber et al. (4) in which no patients (0 of 18) had bacteremia after NT intubation.

The present study was designed to eliminate preexisting oropharyngeal infections as a factor, as well as to determine if there was a relationship between trauma to the nasal mucosa during intubation and the development of bacteremia. There was a small but clinically important risk of bacteremia associated with intubating a patient by the NT route, as seen in positive blood cultures obtained in three of 54 patients. As all patients who proved to be bacteremic were intubated without any discernible trauma, it is possible that the portal of systemic bacterial invasion is the tracheal mucosa. After the endotracheal tube has picked up nasopharyngeal commensals, it may abrade the tracheal mucosa and introduce microorganisms into the circulation at the level of the trachea.

Patients at risk for endocarditis need prophylaxis against α-hemolytic streptococcal bacteremia prior to nasal intubation as they would for operations on the upper airway (9). It is noteworthy that two of our 54 healthy patients had a *Streptococcus viridans* bacteremia. Even when atraumatic, nasotracheal intubation can still be accompanied by the development of bacteremia. Similarly, the use of topical vasoconstrictors does not decrease the risk of bacteremia.

In summary, blood cultures were obtained from 54 patients undergoing elective orofacial surgery before and 2 and 10 min after nasotracheal intubation. Vasoconstrictors were topically applied to the nasal mucosa prior to intubation in 27 patients. In three of the 54 patients bacteremia was present. None of these bacteremic patients had nasal trauma during the intubation and two had topically applied vasoconstrictors. Organisms present were nasopharyngeal commensals incriminated in both endocarditis and systemic infection. We conclude that nasotracheal intubation poses a risk for bacteremia and that the risk of such bacteremia does not appear to be related to trauma to the nasal mucosa during intubation and was not prevented by use of topically applied vasoconstrictors in this study.

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Pulmonary Dysfunction during One-Lung Ventilation Caused by HLA-Specific Antibodies against Leukocytes

Andre M. De Wolf, MD, Bert W. Van Den Berg, MD, Hans J. Hoffman, MD, and Andre A. Van Zundert, MD, PhD

Transfusion-related pulmonary dysfunction caused by leukocyte antibodies has been described (1–11). This reaction is attributable to the action of isoantibodies against leukocytes, which causes cellular aggregation, microvascular occlusion, and capillary leakage. The present report discusses such a reaction that occurred intraoperatively in a patient during prolonged one-lung ventilation. Interestingly, preferentially the noncollapsed lung was injured and the collapsed lung showed only minimal radiologic signs of edema after reexpansion.

Case Report

A 42-yr-old man was scheduled for a transthoracic anterior spondylodesis (Th8–Th12) using the Zielken-Slot technique. The patient had been admitted about 1 month previously, after multiple trauma caused Th9, Th10, and Th11 vertebral compression fractures, creating a kyphosis and some narrowing of the spinal canal, but without neurologic injury. He also sustained a tibial fracture that required open reduction and internal fixation, as well as rib fractures (second through fifth, left) complicated by a left-sided pneumothorax that necessitated placement of a chest tube, and mild bilateral pulmonary contusion that required supplemental oxygen for 1 day. Pulmonary function recovered quickly, and the chest x-ray returned to normal within 48 hr.

After induction of anesthesia, the trachea was intubated with a 39-F left-sided polyvinyl chloride double-lumen endobronchial tube without difficulty. Good position was confirmed by auscultation before and after placing the patient into the right lateral decubitus position. One-lung ventilation was considered to be desirable to allow better exposure for the surgeon and to decrease traumatic manipulation of the upper lung. Monitoring included use of a right radial artery catheter, a triple-lumen, balloon-tipped pulmonary artery catheter, and end-tidal CO_2 recording. Arterial blood gas tensions were measured intermittently. A left thoracoabdominal incision was performed with incision of the diaphragm. Initially both lungs were ventilated with a tidal volume (VT) of 800 ml and a frequency of 15/min. Peak airway pressures were about 28 cm H_2O. Pulmonary artery (PA) pressures were 25–30/10–15 mm Hg, with pulmonary capillary wedge pressures (PCWP) of 8–10 mm Hg and central venous pressures (CVP) of 6–8 mm Hg. After thoracotomy, only the right lung was ventilated with 80% oxygen, with the lumen of the tube going to the left lung left open to air. Ventilation was continued with a VT of 600 ml and a frequency of 20 breaths/min, and 5 cm H_2O of positive end expiratory pressure (PEEP) was applied to the lower lung. Peak airway pressure was 40 cm H_2O.

Anesthesia was maintained with enflurane (0.5–1%)–diazepam–fentanyl–pancuronium. Arterial blood gas tensions before and after initiation of one-lung anesthesia revealed adequate oxygenation (Pa_{O_2} between 110 and 150 mm Hg) and normocarbia (Pa_{CO_2} between 36 and 39 mm Hg). The PA pressures, PCWP, and CVP all increased slightly after initiation of one-lung ventilation; arterial pressure remained stable. During the operation, the patient received six units of whole blood to compensate for a total blood loss of 7600 ml. After 5 hr of one-lung ventilation, an arterial blood sample revealed a sudden decrease in oxygenation (Pa_{O_2} 47 mm Hg) with hypercarbia (Pa_{CO_2} 63 mm Hg). At the same time, pulmonary artery pressures increased quickly (50–55/25–30 mm Hg), with a PCWP of 15 mm Hg and a CVP of 12 mm Hg. Arterial systolic blood pressure did not change significantly. Ventilator settings had not been altered prior to this

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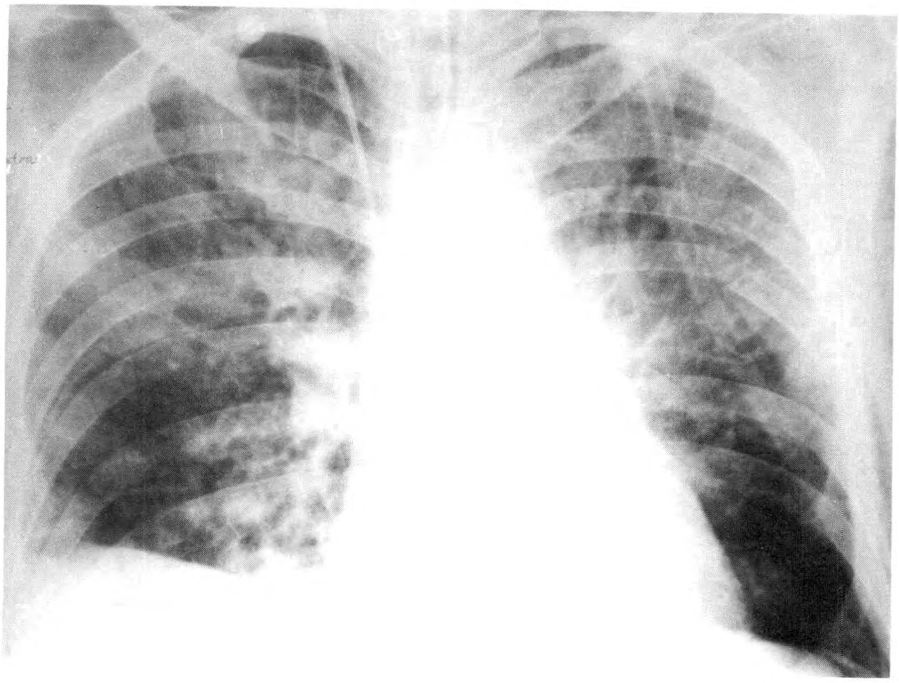

Figure 1. Chest x-ray upon arrival in the intensive care unit, showing diffuse, fine alveolar infiltrates on the left side and patchy, ill-defined infiltrates with some pleural effusion on the right side.

episode, and expiratory minute volume appeared to be unchanged. Immediately, the upper lung was insufflated intermittently with 100% oxygen using a separate Mapleson D system; ventilation to the right lung was kept unchanged. A repeat arterial blood gas tension determination revealed a significantly improved Pa_{O_2} (218 mm Hg), but Pa_{CO_2} changed only slightly (55 mm Hg). Fifteen minutes later, two-lung ventilation was restarted, as surgery was almost completed. Finally, a single-lumen endotracheal tube was inserted without difficulty to allow postoperative ventilation.

The patient was transferred to the intensive care unit (ICU), and ventilated with a V_T of 800 ml, at a frequency of 16/min, an $F_{I_{O_2}}$ of 0.60, and 7.5 cm H_2O of PEEP. Oxygenation was excellent (Pa_{O_2} 187 mm Hg) with slight hyperventilation (Pa_{CO_2} 29 mm Hg). However, upon examination of the chest x-ray taken after arrival in the ICU, the left lung showed diffuse, fine alveolar opacification and the right lung showed a patchy, ill-defined infiltrate, combined with a right-sided pleural effusion (Fig. 1). Harsh breath sounds were heard on auscultation, especially over the right lung. A white blood cell count, preoperative 6400/mm^3, was abnormally low at 3600/mm^3. There were 6% eosinophils in the white blood cell count on arrival in the ICU. The rectal temperature was 39.4°C. The patient was given an intravenous bolus of 100 mg of dexamethasone. The radiologic findings returned to normal over 48 hr, but the left-sided changes, which were less intense, recovered more rapidly than the right-sided changes, as demonstrated by the chest x-ray taken 14 hr after arrival in the ICU (Fig. 2). Clinically, there was an excellent recovery, and the patient was extubated 24 hr after arrival in the ICU. The rest of the postoperative course was unremarkable.

Serologic studies of all involved blood showed that one of the seven donors had human leukocyte-antigen- (HLA-) specific antibodies against leukocytes. This was demonstrated using the lymphocyte-toxicity test. The serum of the recipient did not contain antibodies against granulocytes, and a red blood cell incompatibility could not be demonstrated.

Discussion

Most complications with the use of one-lung ventilation are related to hypoxemia, airway trauma, and malpositioning of the double-lumen tube (12). Hypoxemia is not an uncommon complication during one-lung ventilation, and is mostly caused by the obligatory right-to-left shunt through the nondependent lung. It has been advised that high concentrations of inspired oxygen be used together with low levels of PEEP to the dependent lung, thus avoiding overdistension of this lung (12).

Following these general guidelines, we achieved excellent oxygenation and CO_2 removal during at least 4 hr of one-lung ventilation. However, after this period of excellent oxygenation, hypoxia suddenly occurred, concomitant with hypercarbia. This was preceded by a rapid increase in pulmonary artery

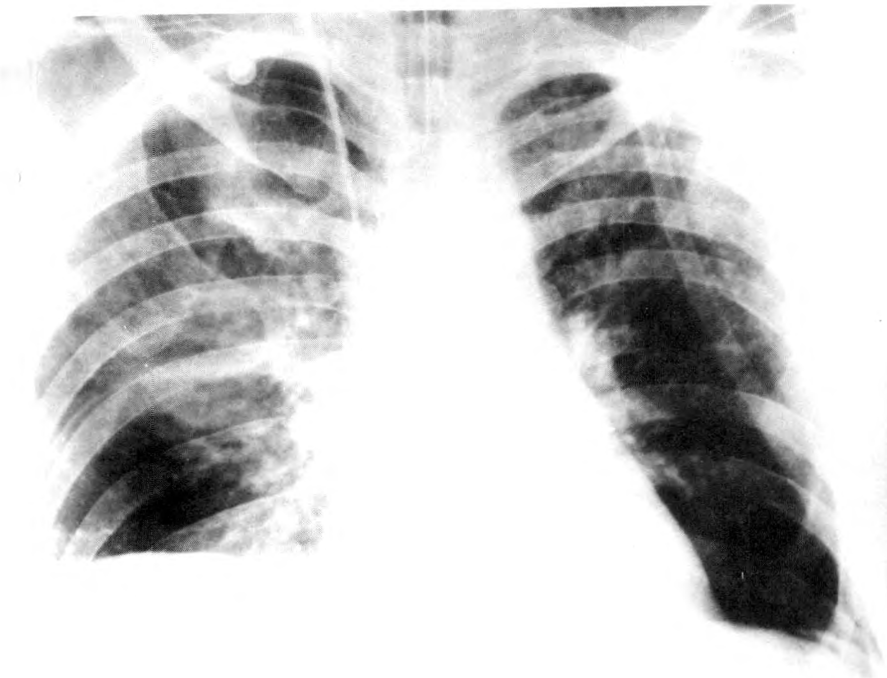

Figure 2. Chest x-ray 14 hr after arrival in the intensive care unit, showing almost complete disappearance of the infiltrates on the left side whereas the patchy infiltrates on the right side are still present.

pressures. The PCWP remained essentially unchanged. The gradient between diastolic pulmonary artery pressure and PCWP increased, indicating an increase in pulmonary vascular resistance. Postoperatively, the chest x-ray demonstrated alveolar opacification, especially in the dependent lung, without signs of congestive heart failure. These radiological signs and the normal PCWP indicated that this was a case of noncardiogenic pulmonary edema. As other causes of noncardiogenic pulmonary edema were unlikely to be present here, although they could not be completely excluded, serologic tests were ordered to determine whether there was a leukoagglutination reaction. This reaction was included in the differential diagnosis, since three other patients with a leukoagglutination reaction had been observed in this hospital during the previous year. Serologic studies showed that HLA-specific leukocyte antibodies were present in the blood of one of the donors, making it very likely that the observed pulmonary edema was caused by a leukoagglutination reaction. This diagnosis was also supported by the increase in body temperature, the decrease in white blood cell count, and the fast recovery of our patient.

Pulmonary failure caused by antigranulocyte antibodies is a relatively rare condition. Usually the leukoagglutinins are found in the donor blood, acting against recipient leukocytes. Less often, the recipient has antibodies against donor leukocytes (6,8–11,13). This reportedly causes a less severe reaction, and therefore less severe symptoms. Frequently there is only a febrile reaction (10). There are two types of leukocyte antibodies: HLA- and non-HLA-related antibodies. It is unclear whether HLA specificity has a prognostic value (5,7). There seems to be a higher incidence of the presence of leukocyte antibodies in the serum of multiparous females (5,11).

Leukostasis with pulmonary leukocyte sequestration causes obstruction of small pulmonary blood vessels and capillaries and an increase in pulmonary vascular resistance (1). Pulmonary vasoconstriction caused by the release of vasoactive substances may also play a role in the pulmonary hypertension. The reaction further may involve the release of toxic oxygen radicals and proteolytic enzymes (14), causing endothelial damage and capillary leakage, and resulting in perivascular edema. Thus, antibody-mediated granulocyte aggregation occurs in small blood vessels, perhaps with release of inflammatory mediators, or even with the activation of the complement cascade (2–4,6,13,14). In any event, the end result is loss of microvascular integrity, causing edema and hypoxemia (2,3,5,7). It has been suggested that acute lung injury may show a wide range of severity—from permeability noncardiogenic pulmonary edema, which is completely reversible, to adult respiratory distress syndrome, a much more severe pathologic process and one with a high mortality rate (5,15).

A transfusion-related acute lung injury has a sudden onset, usually within a few hours of transfusion. Symptoms initially are nonspecific, such as chills, fever, tachycardia, dyspnea, cough, malaise, rash, back pain, cardiovascular collapse, and urticaria, but soon pulmonary dysfunction and then pulmonary edema develop (1–11). Hypotension is also common. The severity of symptoms may be related to the degree of complement activation and to the underlying cardiopulmonary reserve (4,13). During general anesthesia, objective signs include the development of a pulmonary shunt (1,7), an increase in alveolar dead space (7), and even overt pulmonary edema (1,5). Chest roentgenograms show interstitial and alveolar infiltrates without signs of cardiogenic pulmonary edema (cardiac enlargement, pulmonary vascular engorgement) (1–11). The onset of symptoms is rapid, but clinical signs resolve usually within 36–72 hr without sequelae, if the patient survives (1–11). It has a relatively good prognosis and low mortality, except perhaps in compromised patients, even if its course is protracted.

Our patient recovered very quickly. There may be several explanations for this. First, the pulmonary dysfunction might not have been very severe; not every leukoagglutination reaction results in fulminant respiratory failure. The severity of the symptoms in the operating room can be explained by the decreased reserve in pulmonary function (4,13) as a result of one-lung ventilation, since the hypoxia and hypercarbia were easily reversible by ventilating both lungs using moderate amounts of PEEP.

Second, it is possible that the upper lung was injured less severely by the agglutination reaction, since it has been shown that microemboli are preferentially distributed to the ventilated lung, which receives most of the right ventricular output (16). This may be an explanation for the less severe edema of the upper lung, and also for its faster radiological recovery.

It is also possible that the upper lung was barely injured by the leukocyte agglutination reaction, but that the edema was caused by a different, less severe phenomenon—namely, reexpansion pulmonary edema. Although classically reexpansion pulmonary edema is described after lung collapse of long duration (>24 hr) (17), it has been reported that shorter periods of collapse (4 hr) may be followed by reexpansion pulmonary edema (18–20). This type of edema is attributable to increased vascular permeability, caused by vascular stretching during reexpansion (21).

One could say that making the diagnosis of a leukoagglutination reaction is not essential, since therapy is supportive, and not really different from the treatment of complications producing similar findings. However, it must be remembered that a similar, or even more severe, reaction may occur when blood from that donor is transfused to other patients. Similarly, if this patient had been the one with antigranulocyte antibodies, he could suffer again from a leukoagglutination reaction when receiving blood. Such a patient should receive washed red blood cells instead, since the reaction has been described after the transfusion of packed cells (5). These are the reasons why one should persist in making an exact diagnosis.

In summary, we present an uncommon cause of hypoxia during one-lung ventilation, namely, a leukoagglutination reaction associated with transfusion, resulting in noncardiogenic pulmonary edema. Aggressive supportive therapy should lead to complete recovery.

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Preoxygenation Techniques:
Comparison of Three Minutes and Four Breaths

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Administration of 100% oxygen before a "rapid-sequence" induction of anesthesia is recommended to prevent hypoxia during induction. This preoxygenation is particularly important if difficulty with manual ventilation of the lungs or intubation of the trachea is anticipated. Traditionally, preoxygenation for three min or longer is the routine practice (1). However, Gold et al. (2) have challenged the need for a full three min of preoxygenation, suggesting that preoxygenation with four maximal inspirations was equally effective. In this study, we examine whether the two techniques provide comparable protection against hypoxia when apnea follows the induction of anesthesia.

Methods

With approval from our Committee on Human Research, we obtained informed, written consent from 12 subjects undergoing elective surgery. All subjects were ASA physical status 1 and nonsmokers, in whom no difficulties with airway management were anticipated. Subjects randomly assigned to the 4-breath preoxygenation technique ($n = 6$) were instructed to take four maximally deep breaths as soon as the facemask was applied and to continue to take large breaths for as long as possible. Those randomly assigned to the 3-min technique ($n = 6$) were instructed to breathe normally for as long as possible from the time the mask was applied.

Patients were then brought, unpremedicated, to the operating room where a fingertip oximeter probe (Nellcor N-100®) was applied. The oximeter was adjusted to its rapid update mode, i.e., time averaged over 2–3 sec in contrast to the usual 5–7 sec (addendum to the Instruction Manual, Nellcor Pulse Oximeter Model N-100, Nellcor Incorporated, Hayward, CA). *d*-Tubocurarine, 3.0 mg, was administered 3–4 min before the anticipated administration of succinylcholine. All patients breathed 100% oxygen through a Vital Signs® clear facemask, attached to a circle system that had been flushed with oxygen and through which oxygen, 10 L/min, was flowing. After the appropriate period of preoxygenation, anesthesia and paralysis were induced with 4.0 mg/kg thiopental and 1.5 mg/kg succinylcholine. With the onset of apnea, the facemask was removed and no attempts were made to alter the position of the patient's head or jaw. Supplemental doses of thiopental, 1.0 mg/kg, were administered 2 min after the initial dose and then every minute until the completion of the study. Supplemental doses of 0.5 mg/kg succinylcholine were administered 3 min after the initial dose and then every 2 min until the completion of the study. Arterial oxygen saturation (Sa_{O_2}) was recorded before the administration of oxygen, before the induction of anesthesia, and at 15-sec intervals until Sa_{O_2} decreased to 90%. The lungs were then ventilated with 100% oxygen.

Mean times for the two techniques for the onset of apnea and for Sa_{O_2} to decrease to 97%, 95%, 93%, and 90% were compared using a Mann–Whitney *U*-test. A *P* value of <0.05 was considered statistically significant.

Results

Age, height, weight, sex, and preoperative hemoglobins were similar in the two groups, as was the time from administration of thiopental until onset of apnea (Table 1). Arterial oxygen saturation was 99–100% in all subjects after preoxygenation. The times for Sa_{O_2} to decrease to 97%, 95%, 93%, and 90% were more variable but significantly shorter with the 4-breath technique (Table 2).

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Table 1. Demographic Data and Time to Apnea for Subjects Preoxygenated with Two Different Techniques

Preoxygenation technique	Age (yr)	Height (cm)	Weight (kg)	Sex	Hemoglobin (g/100 ml)	Time to apnea (min)
3-min (n = 6)	28 ± 5 (23–37)	168 ± 14 (152–183)	58 ± 13 (45–75)	4F:2M	13.5 ± 1.5 (12.0–16.3)	0.6 ± 0.1 (0.5–0.6)
4-breath (n = 6)	30 ± 4 (25–35)	175 ± 10 (163–193)	66 ± 10 (50–79)	4F:2M	13.4 ± 1.5 (12.1–15.4)	0.4 ± 0.2 (0.2–0.7)

Values are mean ± SD, range in parentheses.

Table 2. Times to Arterial Desaturation for Subjects Preoxygenated with Two Different Techniques

Preoxygenation technique	Time to 97% saturation (min)	Time to 95% saturation (min)	Time to 93% saturation (min)	Time to 90% saturation (min)
3-min (n = 6)	7.9 ± 0.8 (7.2–9.5)	8.4 ± 0.8 (7.8–10.0)	8.6 ± 1.0 (7.8–10.5)	8.9 ± 1.0 (8.2–11.0)
4-breath (n = 6)	5.6 ± 1.4[a] (3.2–7.1)	6.0 ± 1.4[a] (3.6–7.4)	6.3 ± 1.5[a] (3.8–7.6)	6.8 ± 1.8[a] (4.0–9.0)

Values are mean ± SD, range in parentheses.
[a] Significantly different from 3-min ($P < 0.05$ by Mann–Whitney U-test).

Discussion

During induction of anesthesia, many factors (e.g., airway obstruction, hypoventilation, and anesthetic-induced apnea) may result in hypoxia. Drummond and Park (3) demonstrated that patients who breathed air before the induction of anesthesia with thiopental and succinylcholine and whose lungs were not ventilated after receiving these drugs, developed hypoxemia (SaO_2 ranging from 76–95%) within 60 sec. To increase the amount of oxygen available (oxygen reserve) and thus prevent hypoxia during induction of anesthesia, 100% oxygen is often administered to the patient. Traditionally, 3–5 min of preoxygenation has been recommended to ensure an adequate oxygen reserve during a "rapid-sequence" induction of anesthesia. Three minutes is used because of the observation by Hamilton and Eastwood (1) that denitrogenation of the lungs is more than 95% complete in 3 min or less in subjects breathing through a circle system with a fresh gas flow of 4 L/min. Preoxygenation for 5 min was recommended by Dillon and Darsie (4) to prevent hypoxemia after the administration of thiopental; however, they did not examine whether shorter periods were sufficient.

Recently, Gold et al. (2) demonstrated in awake patients that preoxygenation with either 5 min of breathing at normal rates and tidal volumes, or four "maximally deep breaths", produced comparable increases in arterial oxygen tension (PaO_2) and oxygen content. In addition, Gold and Muravchick (5) demonstrated that the PaO_2 in patients who took four maximal breaths of oxygen before the induction of anesthesia increased above that of patients who breathed air before induction. They measured PaO_2 after laryngoscopy and again after intubation of the trachea. Subsequently, Norris and Dewan (6) compared 3-min and 4-breath preoxygenation in pregnant women undergoing a rapid-sequence induction for cesarean section and found that oxygenation of maternal and fetal blood was comparable with the two techniques. However, the duration of apnea in these subjects, although not reported, was presumably short. In addition, measurements of fetal oxygenation were obtained from umbilical cord blood taken at delivery, at which time mothers in both groups had breathed 50% oxygen for at least 2 min (personal communication, Mark Norris, MD). Thus, the extent to which the choice of preoxygenation technique for the mother influenced fetal oxygenation is difficult to assess. It is unlikely that either technique would have an impact on fetal oxygenation.

We found that patients rendered apneic after preoxygenation with four breaths had more rapid onset of, and a more variable time to, arterial oxygen desaturation than did patients preoxygenated for 3 min. There are several possible explanations for our results. First, it is likely that the inspired oxygen concentration was lower in the four-breath group than in the 3-min group, because of the rebreathing characteristics of a circle system. Hamilton and Eastwood (1) demonstrated that at 28.5 ± 6.9 sec after administering 10 L/min of 100% oxygen through a circle system, expired nitrogen concentration was 30% but by 144 ± 24 sec, it was only 5%. In our subjects taking maximal inspirations (four-breath technique), minute ventilation would markedly exceed the fresh-gas flow of 10 L/min; consequently, rebreathing of expired gas will occur (7), decreasing the inspired oxygen concentration. In contrast, in our subjects using the 3-min technique, minute ventilation would be lower than fresh gas flow and inspired gas would be 100% oxygen. This would result in a higher alveolar P_{O_2} and oxygen reserve in the 3-min group.

Second, we estimated oxygen reserve by measuring the time required for arterial desaturation to occur after induction of anesthesia. Other investigators have estimated oxygen reserve indirectly by measuring Pa_{O_2} (2,5,6). However, factors other than Pa_{O_2} at the completion of preoxygenation may influence oxygen reserve. For example, if a patient's lung volume is below functional residual capacity, which is more likely to occur with the 4-breath technique because these patients may actively exhale immediately before the onset of apnea, and if the patient's airway remains patent, elastic recoil of the chest wall might result in entrainment of air, diluting the oxygen content of the lung and decreasing oxygen reserve.

It is also possible that subjects studied by other investigators were better coached than ours at taking maximal inspirations. If this is true, it would suggest that the four-breath technique depends on patient skill and cooperation, which would decrease its reliability.

In summary, we found that Sa_{O_2} decreased more rapidly in patients preoxygenated with four breaths compared with those preoxygenated for 3 min. Although healthy patients undergoing routine anesthetic induction receive adequate protection against hypoxia with four maximal inspirations of oxygen (as evidenced by our finding that the shortest time to desaturation was 4.0 min), patients in whom a prolonged period of apnea might occur after induction of anesthesia should probably breathe oxygen for at least 3 min before the administration of anesthetic drugs.

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Emergency One-Lung High-Frequency Positive-Pressure Ventilation (HFPPV)

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Narrowing of the upper respiratory airways is often extreme before symptoms appear. Three of five patients with primary tracheal tumors at our institution had to be intubated acutely because of rapid development of severe asphyxia. This report describes the use of high-frequency positive-pressure ventilation (HFPPV) as an emergency procedure in such a patient, who previously had had a left pneumonectomy.

Case Report

A 33-year-old man had had a left pneumonectomy 4 yr previously because of sarcoma. Small islands of the tumor were found in the mucosa distally in the main bronchus at some distance from the main tumor. Recovery was uneventful.

He was now admitted because of increasing shortness of breath. Tomography and bronchoscopy showed the distal trachea to be almost occluded by a tumor (Figs. 1, 2*A*, 2*B*). Because of rapidly developing asphyxia, ventilatory support had to be instituted. Under general anesthesia (intravenous fentanyl and an intravenous infusion of methohexital and succinylcholine), rigid bronchoscopy was performed. The tumor was visualized and a catheter (diameter 5.3 mm) with distal side holes was passed down the bronchoscope and past the tumor into the right main bronchus. HFPPV was started through the catheter using a low-compression system with a fixed ventilatory frequency (60/min) and relative insufflation time ratio (22%). The gas mixture consisted of 40–100% oxygen in air. With an inflow volume of 15 L/min, however, the expiration passage was insufficient and hyperinflation of his lung was noted. The ventilator used was so designed that if intratracheal pressure exceeds 20 cm H_2O, ventilation is discontinued. Not until a small outflow catheter had been introduced into the main bronchus to prevent positive pressure distal to the tumor did ventilation become adequate. The bronchoscope was then removed and the anesthetics discontinued. Subsequent HFPPV was well tolerated with little need for sedatives or tranquilizers. Chest x-rays and arterial blood gas tensions showed good gas exchange and no signs of atelectasis.

About 14 hr later, while still on one-lung HFPPV, he was taken to the operating room for resection of the tracheal lesion. Blood gas data during the procedure were as shown in Figure 3. Operating conditions were excellent without the interference of a moving lung. Four centimeters of the distal trachea with the tumor was resected, and a primary end-to-end anastomosis was easily performed via a right thoracotomy. Upon opening of the trachea, the bronchial mucosa was found to be dry, bright red, and covered with crusts near the tip of the catheters. The outflow catheter was almost obstructed by inspissated secretions. The bronchial tree was repeatedly irrigated with saline and the crusts were removed. At completion of the anastomosis, the catheters were withdrawn and ventilation resumed through a nasotracheal tube (Portex no. 7). The patient was able to breathe spontaneously 4 hr after the end of the operation and was extubated.

The postoperative course was uncomplicated. The tumor was a sarcoma of the same type as that previously removed from the left lung.

The patient subsequently underwent three major thoracic operations for recurrences of the disease with conventional intermittent positive-pressure ventilation (IPPV). He was given radiotherapy and chemotherapy. Nevertheless, he died suddenly almost 7 yr after the first operation and 30 months after the tracheal resection. No autopsy was performed, but no stenosis of the anastomosis or local recurrence had been observed.

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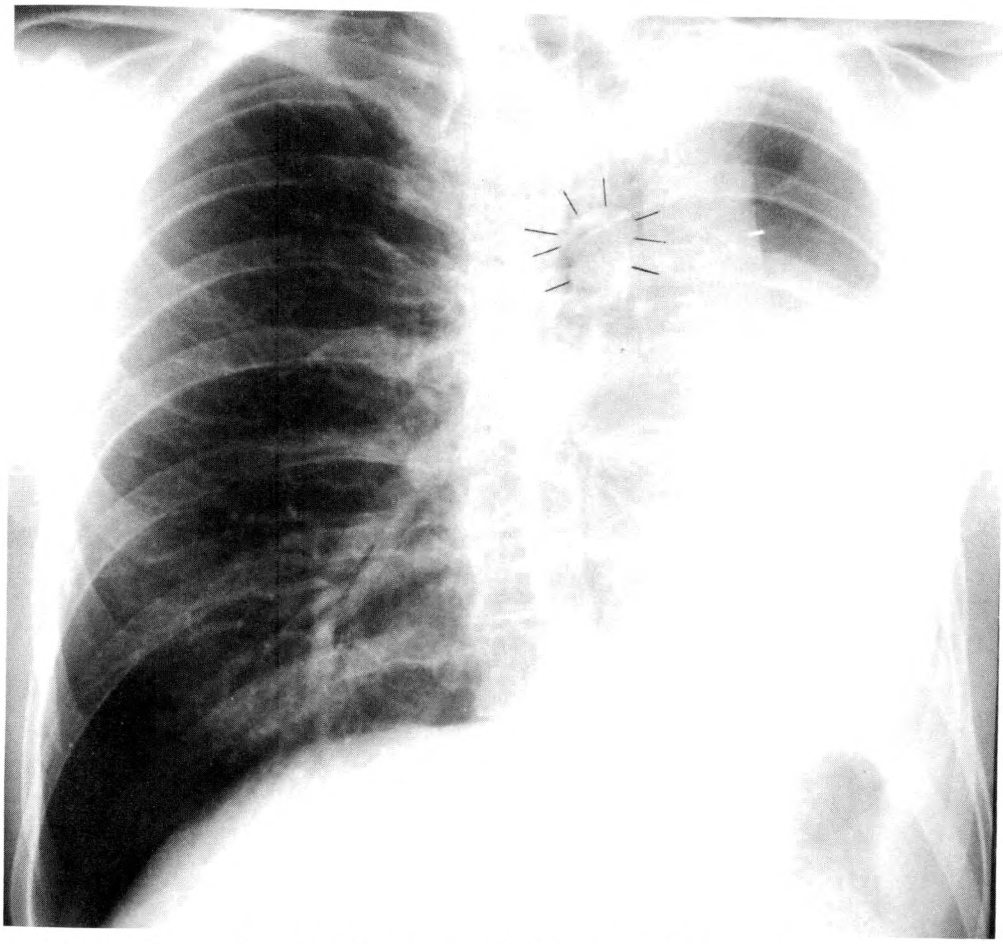


Figure 1. Chest x-ray showing the tumor in the distal trachea. Tracheal deviation to the left as a result of the previous left pneumonectomy was enhanced by the tumor in the trachea, causing air trapping and hyperinflation of the remaining right lung.

Discussion

A method of ventilation frequently used during tracheal surgery utilizes endotracheal tubes and IPPV. After opening the trachea and resecting the obstructing tumor or stenosis, the tracheal tube is passed down into the distal portion of the airways. Alternatively, the airway can be managed by insertion of another (sterile) tube by the surgeon through the incision into the trachea. This tube, however, has to be removed during anastomosis of the cut ends of the trachea and an oro- or nasotracheal tube passed beyond the area resected into the distal airways. This method is clumsy, makes surgery difficult, and is associated with poor control of ventilation.

An alternative method is the use of HFPPV. Originally introduced by Heijman et al. (1), HFPPV has been said to achieve adequate ventilation with tidal volumes that are smaller than anatomic dead space and thus smaller than tidal volumes used for conventional volume-controlled ventilation. HFPPV also is associated with fewer circulatory side effects. Thin-walled endotracheal HFPPV catheters facilitate the surgical access to the airway, and the technique has been widely used for bronchoscopy and laryngeal microsurgery (2).

Although HFPPV has been successfully practiced in open-chest surgery, including management of surgical resection of stenotic areas in the major airways (3–5), HFPPV in such instances is required for a few hours only during the operative procedure. To our knowledge, HFPPV had not previously been used in the preoperative procedure to manage ventilation involving a tracheal obstruction from an occluding tumor. As he had only one lung, management of the patient in the present report was especially difficult.

After admission to the hospital, the patient deteriorated rapidly, became anxious, and had obvious ventilatory problems. For technical reasons, the tracheal operation had to be postponed, and in the meanwhile assisted ventilation had to be instituted. Knowledge that the tumor almost occluded the distal

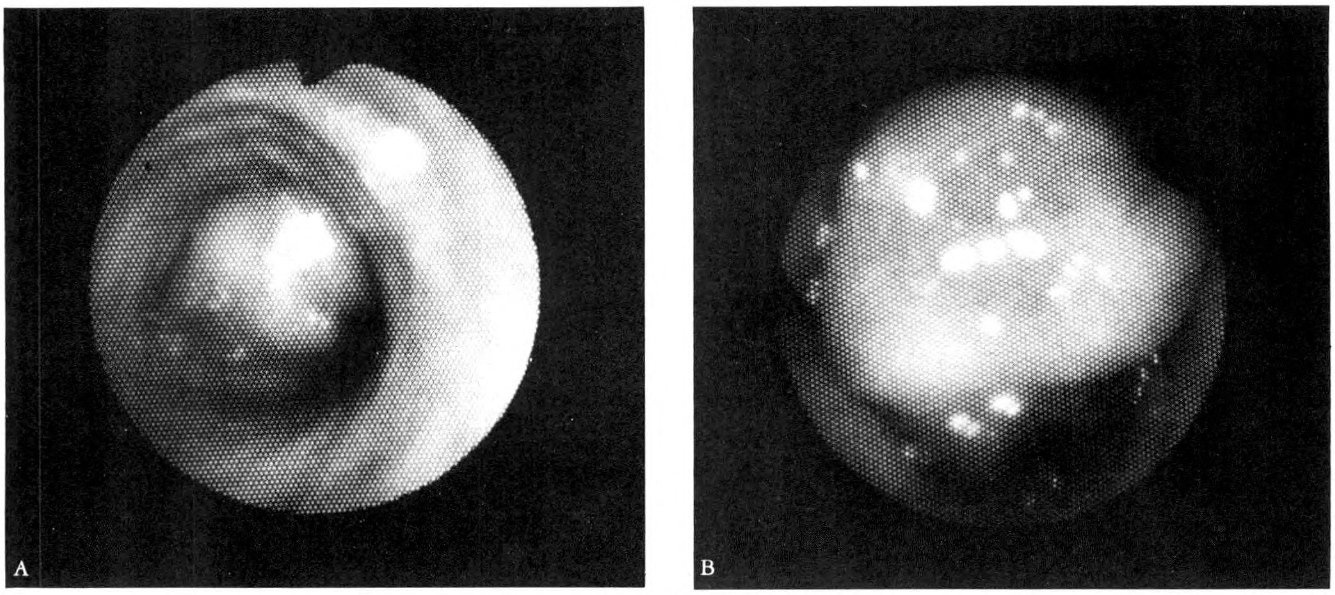
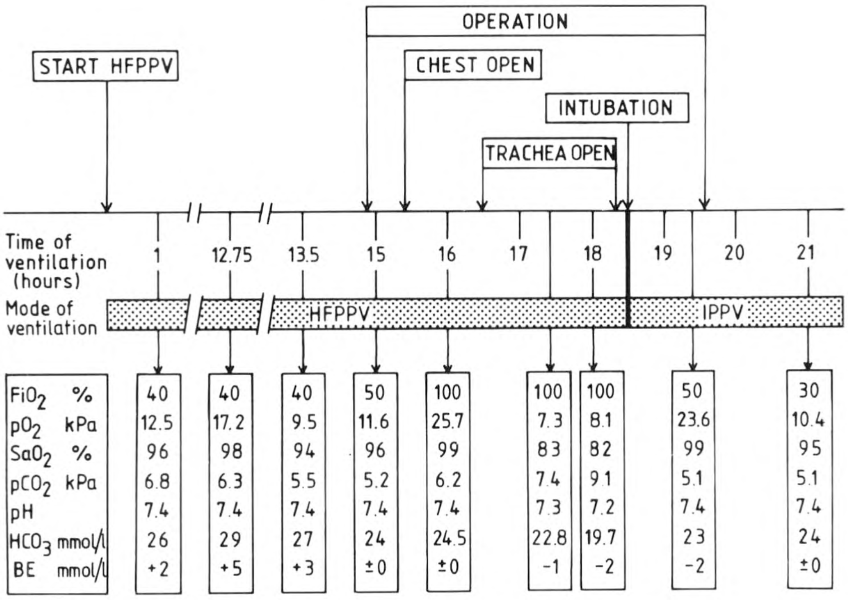


Figure 2. (**A**) The distal trachea with the tumor in situ as seen through the bronchoscope. (**B**) The tumor almost occludes the lumen.



FiO_2 %	40	40	40	50	100	100	100	50	30
pO_2 kPa	12.5	17.2	9.5	11.6	25.7	7.3	8.1	23.6	10.4
SaO_2 %	96	98	94	96	99	83	82	99	95
pCO_2 kPa	6.8	6.3	5.5	5.2	6.2	7.4	9.1	5.1	5.1
pH	7.4	7.4	7.4	7.4	7.4	7.3	7.2	7.4	7.4
HCO_3 mmol/l	26	29	27	24	24.5	22.8	19.7	23	24
BE mmol/l	+2	+5	+3	±0	±0	-1	-2	-2	±0

Figure 3. Diagram of operative and ventilatory conditions during emergency one-lung HFPPV for almost 19 hr.

trachea, and the possibility of causing bleeding from the tumor, made conventional intubation and IPPV less suitable than HFPPV. With one lung only, the anatomical condition of the right lung with a very short main bronchus meant that positioning of an endotracheal tube necessarily would have to be very precise so as not to occlude the upper lobe bronchus. For these reasons, HFPPV with a thin catheter seemed to be an attractive option. We felt it would be safer if bronchoscopy were performed and the insufflation catheter inserted past the tumor under visual control. When HFPPV was started, however, the airway was too small to allow exsufflation and the lung became hyperinflated. A second catheter, which bypassed the tracheal obstacle, was inserted to facilitate expiration. The presence of this second catheter did not interfere with subsequent HFPPV.

HFPPV is normally well accepted by patients (6). This was also seen in the present report; the patient tolerated HFPPV for 14 hr with very little need for sedatives. In spite of long-term low airway pressure associated with this technique, he did not develop atelectasis; chest x-ray was normal and blood gases showed good oxygenation.

During surgery via a right-sided thoracotomy, HFPPV was continued but adequate oxygenation and ventilation were more difficult to maintain. An increase in $F_{I_{O_2}}$ to 50–100% restored Pa_{O_2} to normal values for the major part of the operation, but progressive arterial acidosis developed. The impaired gaseous exchange may in part have been related to compression of lung tissue caused by the surgical manipulations. The lung was still more likely to deflate when the main bronchus was open. During this part of the operation, it was more difficult to ventilate the lung and to maintain adequate gaseous exchange. However, this type of ventilation provided excellent surgical access to the trachea, and the operating time could be shortened accordingly.

The anatomical condition of the right lung created a problem with the correct placement of the catheter and may have contributed further to ventilation insufficiency. The right upper lobe bronchus arose at the most a few centimeters from the resection border. To prevent the HFPPV catheter from coming out of the main bronchus because of pressure waves set up by the insufflation, the catheter had to be placed deep into the bronchus, thus risking inadequate ventilation of the upper lobe. The positioning of the catheter tip was of vital importance, particularly in the right lung. Possibly the catheter could have been sutured temporarily to the bronchus to overcome this problem. Alternatively, the problem could have been solved by ventilation through two catheters. In addition to a catheter deep in the bronchus, a second catheter could be placed more proximally to provide for the ventilation of the upper lobe.

Upon opening of the main bronchus in the present case, the mucous membrane was found to be dry and covered by crusts. Surprisingly little attention has been paid to this problem in clinical practice. The high gas flow involves the risk of desiccation of bronchial mucosa. The damage will increase with increasing duration of ventilation. With prolonged use of high-frequency ventilation, adequate humidification of the gas mixture is necessary. The equipment we used has no humidifier, though several techniques have been employed during high-frequency ventilation to assure humidification (7) and would have been beneficial in the present case.

The present case demonstrates that, if certain precautions are taken, it is possible with HFPPV to achieve adequate endobronchial ventilation for a considerable period of time and the method may be livesaving in patients with severe asphyxia because of tracheobronchial obstruction.

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Treatment of Intrathecal Morphine Overdose by Aspiration of Cerebrospinal Fluid

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Intrathecal morphine provides selective analgesia for postoperative and chronic pain. However, numerous case reports describe respiratory depression associated with use of intrathecal morphine (1). Although most cases can be safely and effectively treated with naloxone (2), we describe a case of intrathecal morphine overdose treated by aspiration of cerebrospinal fluid (CSF) and instillation of normal saline.

Case Report

An 81-yr-old, 45-kg, 150-cm man was scheduled for elective left hemicolectomy for repair of a recurrent sigmoid volvulus. The patient had a history of two previous myocardial infarctions (the most recent, 4 yr before this admission), severe three-vessel coronary artery disease inoperable because of poor distal vessels, and congestive heart failure.

The patient was premedicated with oral diazepam (5 mg). Radial artery and pulmonary artery catheters were inserted. A spinal catheter was inserted at the L3–4 interspace using a paramedian approach and free flow of CSF was demonstrated. Using 1% lidocaine, continuous spinal anesthesia to a T-6 sensory level was obtained. General anesthesia was induced with 75 mg thiamylal and the trachea was intubated after intravenous administration of 100 mg succinylcholine. Anesthesia was maintained with a low concentration of isoflurane and oxygen. The operation was uneventful and the patient remained hemodynamically stable. Two hours before the end of surgery, 0.75 mg of morphine in a volume of 1.5 ml was administered intrathecally via the spinal catheter. When surgery was completed, the trachea was extubated and the patient taken to the surgical intensive care unit. On arrival, he was awake and alert and complained of pain at the surgical site. Intravenous morphine, 3 mg, administered in divided doses, eventually provided pain relief. The spinal catheter was left in place.

The following morning, the patient again complained of pain at the surgical site. Accidentally, 5 mg of morphine in 10 ml was administered via the spinal catheter rather than the intended 0.5 mg. The patient obtained excellent pain relief. Four hours later he became markedly somnolent. At this time, the accidental overdose was discovered. An arterial blood sample obtained while the patient was breathing oxygen via a nasal cannula (5 L/min) showed pHa to be 7.36, Pa_{O_2} 129 mm Hg, and Pa_{CO_2} 40.5 mm Hg; prior to the intrathecal dose of 5 mg, pHa was 7.46, Pa_{O_2} 145 mm Hg, and Pa_{CO_2} 33 mm Hg.

As the patient became more obtunded, we decided to aspirate CSF through the spinal catheter to remove the excess morphine. Within 10 min, a total of 50 ml of CSF was removed. The patient complained of a mild headache. Sterile normal saline (50 ml) was then instilled into the CSF over a period of 6 min. When this injection was complete, the patient was fully awake and had no headache. He complained of severe pain at the surgical site and bilateral lower leg cramps. Intravenous morphine, 7 mg, was administered, but did not provide relief. Intrathecal morphine, 1 mg, was then reintroduced, in divided doses, providing excellent pain relief without sedation or evidence of respiratory depression. An arterial blood sample obtained 4 hr later indicated a pHa of 7.38, Pa_{O_2} of 104 mm Hg, and Pa_{CO_2} of 31 mm Hg.

Discussion

Management of respiratory depression secondary to intrathecal morphine requires close monitoring of respiratory status and possible treatment with naloxone. Although naloxone provides safe and effective treatment for these side effects, we were concerned that the effects of the large dose of morphine administered to this relatively small patient might be too prolonged

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and lead to an extensive stay in the intensive care unit. Therefore, we chose to remove CSF and replace it with normal saline. The result of this treatment was a rapid correction of both respiratory and central nervous system depression. The technique of withdrawing CSF to control the level of spinal anesthesia induced with procaine was described in 1942 by Lemmon and Paschal (3). To our knowledge, ours is the first reported case using the same technique to control the concentration of intrathecal morphine.

Our results raise several questions. First, did the rapid reversal of adverse effects in our patient result from the actual removal of morphine from the subarachnoid space, or from changes in volume and pressure within the subarachnoid space due to removal of CSF and/or instillation of saline? Although we did not directly measure the amount of morphine withdrawn, it is likely that the 50 ml of CSF removed contained much of the administered dose. Morphine is hydrophilic (2); thus, a major portion of any intrathecally administered dose remains in the spinal fluid. Furthermore, the volume of distribution of intrathecal morphine is approximately one half the total volume of CSF (4), which is approximately equal to the spinal CSF volume. It is therefore likely that the removal of 50 ml of CSF in our patient (the approximate equivalent of his spinal CSF volume) removed a large portion of the 5-mg intrathecal morphine dose. This would explain the observed rapid reversal of adverse effects.

If spinal CSF retains a higher concentration of morphine than supraspinal morphine, as suggested by Nordberg et al. (4), then withdrawing CSF from the lumbar area may have produced a bulk flow of CSF from the supraspinal centers that diluted the morphine concentration in spinal CSF and decreased the degree of analgesia. The pain the patient experienced after aspiration of CSF was specific to the surgical site, i.e., it was the same pain experienced before receiving intrathecal morphine, and was relieved only after reinjection of a 1-mg intrathecal dose. If the pain had been caused by the instilled saline, or by changes in CSF pressure or volume, we would have expected to find generalized, nonspecific pain because pain fibers beyond those of the surgical wound site would have been stimulated.

Our patient did complain of bilateral lower leg cramps. However, he had a history of leg cramps regularly treated with quinine sulfate. The leg cramps experienced after removal of intrathecal morphine were probably an aggravation of this chronic condition, and may have been precipitated by hyperventilation and a lowered ionized fraction of calcium due to the patient's agitated state. Although Lucas et al. (5) reported that intrathecal injection of hypertonic saline commonly produced muscle spasms, they did not indicate the concentrations of "hypertonic saline" used. There are no reported adverse effects from the intrathecal injection of normal saline at room temperature.

Second, what is the effect of sodium chloride on the effects of intrathecal morphine? The replacement of CSF by an equal volume of normal saline would dilute any morphine remaining in the subarachnoid space. It would also maintain the total CSF volume and pressure, and thus reduce the risk of spinal headache. In addition to these direct effects, in vitro studies have demonstrated that low concentrations (1 mM) of sodium may impair the binding of opiate agonists to opiate receptors (6). The concentration of sodium in CSF is approximately equal to that in plasma (7). Instilling normal saline, which has a sodium concentration of 154 mEq/L, into the subarachnoid space of a patient whose serum sodium is 138 mEq/L would increase the CSF concentration of sodium to a level that might impair morphine binding to appropriate receptors. Thus, the increased CSF sodium concentration in our patient may have contributed to the observed rapid reversal of adverse effects.

Third, what are the implications of our observations for the site of action of intrathecal morphine? The major site of action of spinal opioids is thought to be in the substantia gelatinosa within the dorsal horn (2). In our case, the speed with which the aspiration and replacement of CSF with normal saline reversed the toxic effects of intrathecal morphine is consistent with the possibility that spinal opiates also have an effect upon the spinal roots and ganglia (8). The diffusion of morphine from the substantia gelatinosa would take much longer than could account for the rapid reversal of effects observed in our patient.

In summary, we describe a case in which aspiration of CSF and intrathecal instillation of normal saline quickly reversed respiratory and CNS depression caused by an overdose of intrathecal morphine. We propose the following mechanisms to explain this effect: direct removal of intrathecal morphine in spinal CSF, dilution of any remaining morphine by normal saline and by bulk CSF flow from supraspinal centers, and displacement of morphine from its receptors by a saline-induced increase in the CSF concentration of sodium. We conclude that intrathecal aspiration of CSF and instillation of normal saline is an effective alternative treatment for an overdose of intrathecal morphine.

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Anesthetic Management of Pheochromocytoma Resection during Pregnancy

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Pheochromocytoma during pregnancy has been reported in 128 cases in the world literature. In only 33% of these cases was the diagnosis made before delivery (1). Overall maternal and fetal mortality rates have been reported at 48 and 55%, respectively (2). Although it has generally been recommended that before the third trimester, the treatment of choice is resection of the tumor (1–3), there has been little documentation to support this viewpoint. Moreover, despite several reports (4–9) of anesthetic management of these cases at parturition, reports of management before the third trimester are absent from anesthetic literature.

Case Report

A 29-yr-old pregnant woman, gravida 2, para 1, presented at approximately the twentieth week of gestation (confirmed by ultrasound) with hypertension of 180/110 mm Hg. Admission ECG showed normal sinus rhythum without ectopy. She denied headache, blurred vision, excessive weight gain, dependent edema, or previous problems with high blood pressure. The course of her initial pregnancy was unremarkable other than for placenta previa diagnosed during labor and resulting in emergency cesarean section with delivery of a normal neonate. Her remaining past medical history was noncontributory. Initial physical examination and routine laboratory values were unremarkable. Fundal height was 19 cm and fetal heart tones were present. Medications included prenatal vitamins. Presumptive diagnosis was hypertension of unknown etiology, with pregnancy-induced hypertension to be ruled out.

Subsequent urinary studies revealed normetanephrine to be 8.5 ng/24 hr (normal 0–0.9), metanephrine 0.1 (normal 0–0.4), vanillylmandelic acid (VMA) 28.19 ng/24 hr (normal 2.5–3.8), and total catecholamines 1989 μg/24 hr (normal 0–280). Abdominal ultrasound revealed an 8-cm right adrenal mass. No other radiologic or invasive studies were performed.

The patient was hospitalized for blood pressure control and preoperative preparation for tumor removal. She was treated with phenoxybenzamine; the initial dose of 10 mg twice a day was gradually increased to a final dose of 20 mg four times a day; and propranolol, the initial dose of 10 mg twice a day being increased to a final dose of 20 mg twice a day. Her blood pressure stabilized in the 160/90 mm Hg range 2 weeks before surgery. During this period she had a normal heart rate without arrhythmias. There were no episodes of postural hypotension, nor did she have a significant anemia. She was brought to surgery at 24 weeks gestation.

The night before surgery the patient received oral cimetidine 300 mg. On the morning of surgery the patient received cimetidine 300 mg and sodium citrate 30 ml orally. Intravenous injection by the anesthesiologist of morphine sulfate 10 mg and diazapam 10 mg was required before the desired state of sedation was achieved. On arriving in the operating room, a right radial arterial catheter was inserted along with a pulmonary artery catheter through the right internal jugular vein. Monitoring included ECG, automated blood pressure measurement, temperature probe, esophageal stethoscope, and external fetal heart rate monitor. After preoxygenation, cricoid pressure was applied and anesthesia induced with thiopental 400 mg plus succinylcholine 100 mg. After tracheal intubation, anesthesia was maintained with fentanyl 750 μg, nitrous oxide 50%, oxygen 50%, and enflurane 0.5–1%. Relaxation was provided with atracurium. A

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minimal amount of trimethaphan intravenous infusion and 2 mg propranolol were required for a postintubation blood pressure of 190/120 mm Hg with a heart rate of 120 beats/min. A nitroglycerin infusion was later required during tumor manipulation when mean arterial pressure reached a maximum of 100 mm Hg. Pulmonary artery pressures remained stable throughout surgery with a wedge pressure of about 23 mm Hg. Estimated blood loss was 700 ml. A total of 5.5 L of crystalloid was given during the 3-hr procedure; urine output was 589 ml. Abdominal exploration revealed an 8 × 10 cm suprarenal mass and a right adrenalectomy was performed. Fetal monitoring revealed no gross aberrations of heart rate during this procedure.

The patient's postoperative course was uneventful, although her hypertension was not completely cured. She was maintained on phenoxybenzamine despite normal urinary VMA/catecholamine levels postoperatively. An elective cesarean section was performed in the 39th week of gestation. Epidural anesthesia was used and the procedure was tolerated with little change in hemodynamic function. A 2977-g male infant was delivered with 1- and 5-min Apgar scores of 9 and 9. Abdominal exploration through the incision revealed no right suprarenal masses nor other evidence of metastatic disease. Subsequent postpartum course has been uneventful for both mother and child, with complete resolution of the maternal hypertension. Urinary metanephrine and catecholamines were both within normal limits 6 months postoperatively.

Discussion

The anesthetic management of pheochromocytoma in nongravid patients has been well-described (10,11). There are, however, additional factors that must be addressed in dealing with pregnant patients with this tumor. These include: 1) effects of drugs and anesthetic agents on uterine activity and the fetus; 2) premature rupture of membranes, complicated by ensuing hypertensive crisis (12), with increased fetal and maternal morbidity and mortality; 3) maternal hypotension, hypoxia, or hypocarbia with resultant placental insufficiency and fetal distress; 4) stresses of anesthesia and surgery resulting in premature labor (13); 5) increased difficulty in tumor definition preoperatively due to restricted radiologic studies for fear of excessive fetal exposure to radiation; 6) increased tumor vascularity during pregnancy (2); 7) controversy in the literature regarding the desirability of surgical or medical management of these patients (14,15); 8) an 11% maternal mortality rate and 50% fetal mortality rate, even in cases with antepartum diagnosis of pheochromocytoma (2).

The cornerstone of medical management remains α-adrenergic blockade with phenoxybenzamine. This drug provides control of the hypercatecholemic state and its associated constriction of the intravascular space that leads to relative hypovolemia and hypertension. The administration of α-blockers results in the restoration of intravascular volume and normal to low vascular tone. Review of cases of tumor excision with delayed delivery revealed a 22% maternal mortality rate and 75% fetal mortality rate in non-α-blocked patients, but no maternal or fetal mortality when α-blockers were used (15).

The preoperative use of propranolol remains controversial. β-Blockers, used only in the presence of α-blockade to prevent exacerbation of hypertension due to unopposed vasoconstriction, may be essential to decrease the hyperdynamic state and to control arythmias. There have been reports associating the use of propranolol with intrauterine growth retardation (16). Moreover, there is concern that β-blockade may cause increased myometrial irritability and premature labor. A recent review, however, suggests that therapy with β-blockers for control of hypertension in pregnancy appears to improve the likelihood that the fetus will be normal (16).

The choice of a potent inhalation agent in these cases seems appropriate as a means to provide uterine relaxation and decrease the possibility of premature labor. It is essential, however, to avoid acute fluctuation in cardiovascular function during anesthesia administration. Exacerbations of hypertension may lead to stroke or acute congestive heart failure. Avoidance of hypertension may be especially difficult if a rapid sequence induction is used on the basis that a pregnant patient is considered to have a "full stomach." Preoperative management of a full stomach should include H_2 blockade and antacids.

General principles of managing any patient with pheochromocytoma must be followed (10,11). These include adequate depth of anesthesia to preclude cardiovascular instability secondary to noxious stimuli, prompt use of potent antihypertensives to aggressively treat hypertensive episodes, control of arrhythmias, and control of hypotension after tumor excision by adequate fluid replacement.

Monitoring of patients with pheochromocytoma requires the use of an ECG, arterial catheter, and Foley catheter. The use of a pulmonary arterial catheter as opposed to a central venus pressure catheter to assess fluid requirements, has also been advocated, because correlation between right atrial pressure and wedge pressure has not always proved reliable in these patients (17).

In summary, a case of pheochromocytoma resection in mid-trimester pregnancy with subsequent elective delivery of a healthy neonate has been described. Prepartum diagnosis of the pheochromocytoma is necessary to improve survival rates in both mother and infant. Surgical excision during the first and second trimesters, with optimal preoperative preparation and perioperative monitoring, should decrease both maternal and fetal mortality rates by minimizing operative risks and drug effects on the mother and fetus.

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Letters to the Editor

Tonic-Clonic Activity after Sufentanil

To the Editor:

The article by Goroszeniuk et al. (1) prompts us to report a recent experience we had with narcotics and seizures. Our patient, a 69-yr-old, 75-kg man with three vessel coronary artery disease was scheduled for coronary artery bypass grafting. Medications included propranolol, 20 mg, four times per day. After premedication with 2 mg lorazepam and 6 mg morphine, the patient was brought to the operating room where ECG leads (chest lead V) were applied and intravenous and intraarterial cannulae placed. While the patient was breathing 100% oxygen by mask, pancuronium, 1 mg, was given, followed by sufentanil, 50 μg. The patient appeared sedated; heart rate was 86 beats/minute and blood pressure 118/70 mm Hg. Shortly after administration of these drugs, tonic-clonic activity of the extremities started. The pupils were small and equal, with conjugate deviation to the right. Movements of the extremities spontaneously ceased in less than 30 sec. Pulse and blood pressure remained unchanged from baseline during the episode. Induction was completed with incremental doses of sufentanil to a total of 1000 μg and pancuronium, 10 mg. No further abnormal movements were observed intra- or postoperatively. The patient was awake with spontaneous movement of all extremities several hours later and was extubated 10 hr postoperatively. No neurologic deficits were present. He had no memory of the event, and his postoperative course was unremarkable.

Grand mal seizure activity has been reported after as little as 100 μg of fentanyl (2). Seizure-like movement with an absence of seizure activity on a simultaneous EEG recording during fentanyl administration has been reported (3). Sebel et al. investigated the effects of high-dose fentanyl on the EEG and found no evidence of seizure activity (4). However, high-dose fentanyl in rats can induce both clinical and EEG evidence of seizures (5). The effects of sufentanil on EEG activity has been investigated by Bovill et al., who found sharp wave activity of unclear significance with no clinical evidence of seizure activity following a dose of 15 μg/kg (6). No previous reports of seizure or seizure-like activity resulting from sufentanil have appeared to our knowledge.

The etiology of the abnormal movement observed by us is unclear. It may represent seizures, myoclonic activity, or an atypical form of rigidity resulting from narcotic administration. Premedication with lorazapam did not prevent its occurrence.

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Esophageal Intubation

To the Editor:

Birmingham et al. (1) recently reviewed techniques to detect a potentially fatal anesthetic mishap namely, esophageal intubation. Detection of a misplaced endotracheal tube is probably more difficult in children than in adults. Chest movement secondary to air in the stomach can easily mimic normal ventilation. Standard auscultation in five places (both apices, both lateral lung fields, and epigastrium) may fail to detect an esophageal intubation, because all sounds are readily transmitted, especially in infants. The use of a Jackson-Rees or a Bain circuit makes measurement of exhaled tidal volumes difficult. Reservoir bag compliance and condensation inside the endotracheal tube are not always reliable. Pulse oximetry may be an earlier indicator in children secondary to their higher oxygen consumption, but the practice of ventilating pediatric patients with 100% oxygen prior to intubation will delay detection of arterial desaturation.

I was recently involved with two cases which illustrate the fact that esophageal intubation may be difficult to diagnose in children. The first patient was a 7-month-old 5-kg male infant with truncus arteriosus type I, undergoing total repair. At the end of the procedure, we elected to change the oral endotracheal tube to a nasal tube for postoperative ventilation. The tube was replaced under direct vision. The second patient was a 5-yr-old undergoing bilateral talo-achilles lengthening. A mask induction was followed by oral tracheal intubation facilitated by muscle relaxation.

In both cases, the intubationist believed the endotracheal tube to be in the trachea. There was bilateral chest movement, and "breath sounds" could be heard over four areas of the chest. However, the epigastrium was also moving and "breath sounds" were not vesicular. These "breath sounds" could also be heard over the epigastrium. No hemodynamic changes or cyanosis were noted, but there was a high index of suspicion of an esophageal intubation. Both patients were immediately extubated, ventilated by mask, and reintubated. Correct placement resulted in an obvious difference in chest expansion and the auscultation of vesicular breath sounds.

Birmingham et al. (1) concluded that "end-tidal" carbon dioxide measurement is . . . perhaps the most reliable means . . . of determining proper tube position." Although this statement may be true, end-tidal CO_2 monitoring is certainly not the standard of care in many operating rooms. A high index of suspicion is probably most important. If there is any question at all, the endotracheal tube should be removed. The patient can then be ventilated by mask before laryngoscopy is repeated with correct placement of the tracheal tube.

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Reference

1. Birmingham PK, Cheney FW, Ward DJ. Esophageal intubation: a review of detection techniques. Anesth Analg 1986;65:886–91.

To the Editor:

"Esophageal Intubation: A Review of Detection Techniques" (1986;65:886–91) was a timely, well-written review. I would like to see added to the authors' list of methods of assessing tube position a simple technique to be utilized by the individual supervising the intubation of an adult patient. If, *during the passage* of the endotracheal tube, the supervisor gently palpates the trachea in the sternal notch or applies cricoid pressure, he or she will appreciate "an old washboard-like" sensation as the tube passes over the corrugations of the tracheal rings. There should be no false positives to this sign because the esophagus is soft and lies posterior to the membraneous portion of the trachea. I have not yet encountered either a false positive or a false negative.

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To the Editor:

The underlying assumption of the paper by Birmingham et al. (1) is a matter of serious concern. Specifically, it is taken for granted that a state of total muscular paralysis must be induced for the purposes of routine tracheal intubation.

The fact is that, for elective procedures, total muscular paralysis not only is not necessary but in fact may be a potentially lethal and totally avoidable phase in the anesthetic process.

Review of data from published reports (2,3) as well as my own 20 years experience with cases coming to litigation all indicate that the majority of cardiac arrests and anesthetic deaths occurring at induction are either 1) the result of inability to intubate and/or ventilate a paralyzed patient or; 2) the end result of continued "ventilation" of a paralyzed patient through an improperly placed tube (i.e., esophageal intubation). This being the case, the inescapable conclusion is that if the patient had not been paralyzed then the catastrophe would not have occurred.

Note that routine "awake" intubation is not advocated. Rather, after adequate topical anesthesia of the upper airways, one administers a small ("sleep") dose of thiopental which is then followed by the administration by mask of a single potent inhalation agent (halothane or enflurane/oxygen can be used but not N_2O), after about 8 min denitrogenation as well as a satisfactory level of anesthesia are achieved. At this time an unhurried tracheal intubation can be performed. (For very muscular patients one may administer a non-paralyzing dose of a non-depolarizing muscle relaxant such as 6.0 mg of *d*-tubocurarine 5 min before the anticipated time of intubation.) If the intubation is successful, when one connects the proximal end of the endotracheal tube to the breathing circuit one sees appropriate movements of the reservoir or breathing bag. If the intubation is not successful, then connecting the proximal end of the tube to the breathing circuit does not result in bag movements but the patient will continue to breathe, bringing great relief to all concerned.

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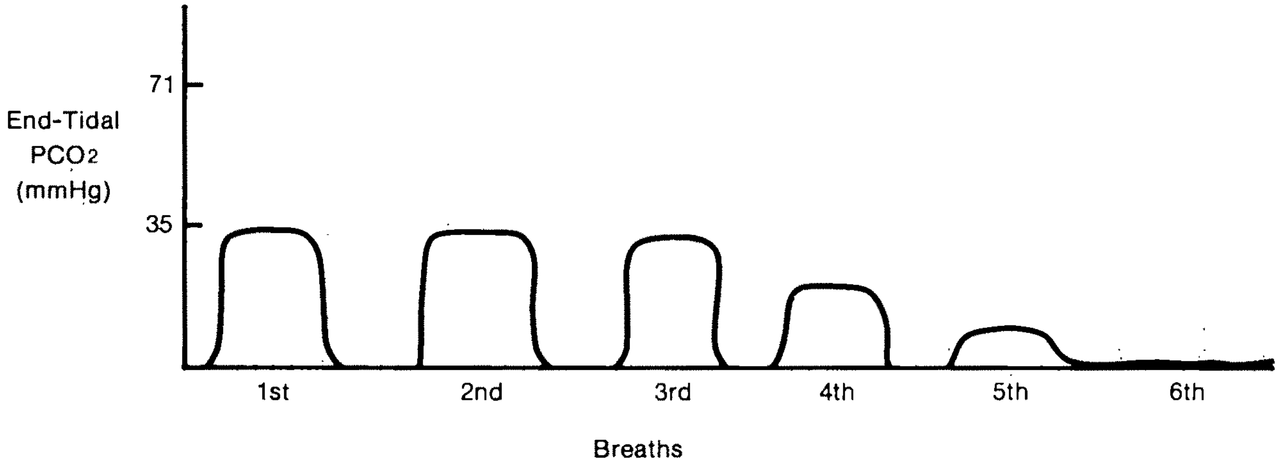

Figure 1. P_{CO_2} waveforms obtained in a 10-yr-old boy with an esophageal intubation. The waveform of the first three breaths looks virtually normal before becoming flat very quickly.

To the Editor:

I read with interest the review article on esophageal intubation by Birmingham et al. (Anesth Analg 1986;65:886–91). I agree with the authors that end-tidal CO_2 measurement is at present the most reliable means under all circumstances of determining proper tube position. But I would like to report a case that demonstrates a limitation of this monitor.

I had a 10-yr-old boy in whom anesthesia was induced with halothane, oxygen, and nitrous oxide. Breathing was assisted, and when anesthesia was deep enough, intubation was performed. The CO_2 waveform on the mass spectrometer (Fig. 1) was checked. Initially it looked no different from that obtained from a proper endotracheal intubation. But the breath sounds did not sound right. As shown in the figure, after three normal CO_2 waveforms, the end-tidal CO_2 very quickly decreased in amplitude. Direct laryngoscopy was performed, and the tube was found to be in the esophagus. The trachea was then quickly intubated and the situation was again in control.

The lesson to learn here is that at least initially, a normal CO_2 waveform can be obtained with esophageal intubation. If enough alveolar gas is forced down the esophagus into the stomach during mask ventilation prior to intubation, the concentration of CO_2 in the latter may be similar to that in the alveoli. Thus, when the stomach is ventilated after the esophageal intubation, an almost normal waveform of CO_2 may be seen. After a few breaths, the CO_2 in the stomach will then be diluted and the waveform will very quickly become flat. I believe this is what happened in this patient.

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Errata

Van Zundert A, Vaes L, Van Der Aa P, Van Der Donck A, Meeuwis H. RAM Testing in Obstetric Patients (letter). Volume 65, Number 11, November 1986.

The authors wish to inform readers of the following:
In the second sentence, change
"The RAM-test is the difference between two RAM-tests."
to read
"The RAM-block is the difference between two RAM-tests."

de Bruijn NP, Croughwell N, Reves JG. Hemodynamic Effects of Esmolol in Chronically β-Blocked Patients Undergoing Aortocoronary Bypass Surgery. Volume 66, Number 2, February 1987.

The authors wish to inform readers of the following:
On page 141, left column, 12 lines from the bottom, change
"concentration of enflurane (0.9%) because we wanted . . ."
to read
"concentration of enflurane (0.4%) because we wanted . . ."

Kempen PM. A Practice of Anesthesia for Infants and Children (book review). Volume 66, Number 3, March 1987.

Gremlins struck!
On page 288, right column, line 11, the sentence should read
"Fig. 20-1 is also erroneous and misleading," most likely due to printing error.

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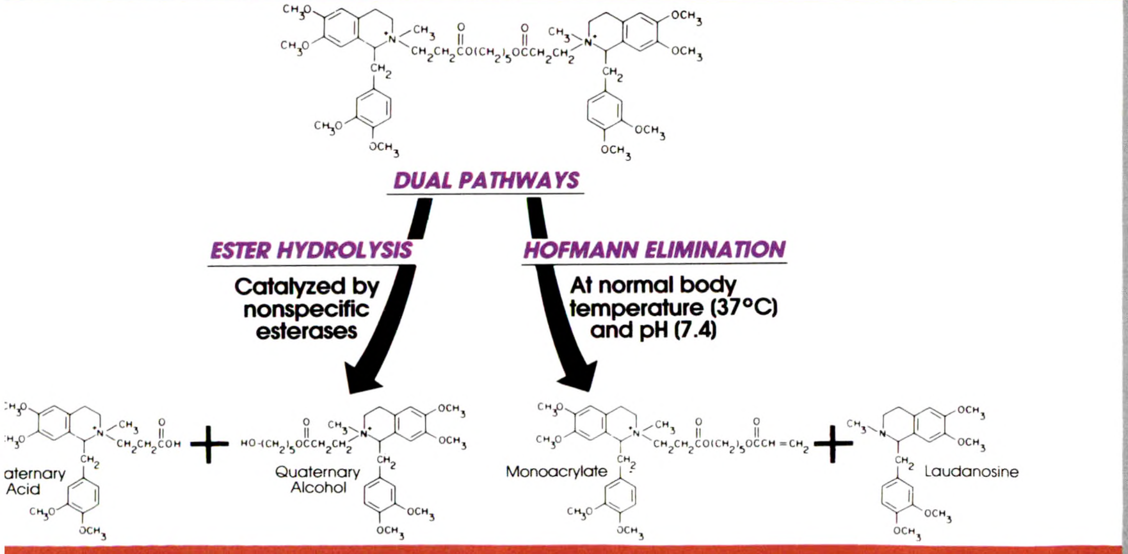

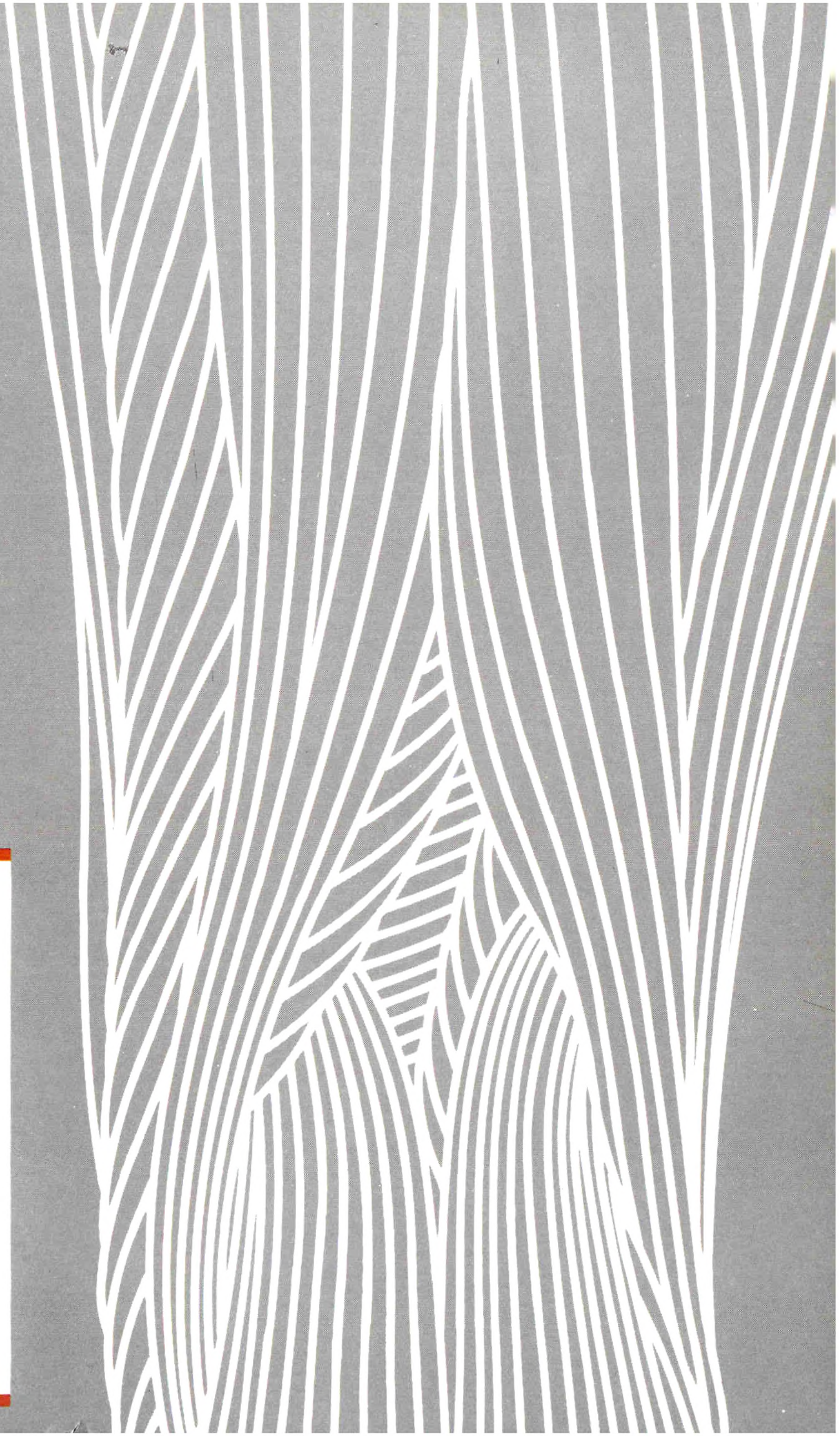

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Tracrium Injection is a less potent histamine releaser than d-tubocurarine or metocurine.

Clinically significant changes (about 200% of control) in arterial pressure and heart rate resulting from histamine release occur well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 x ED_{95}) for metocurine, and outside the clinical dosage range (at 3 x ED_{95}) for atracurium.[1]

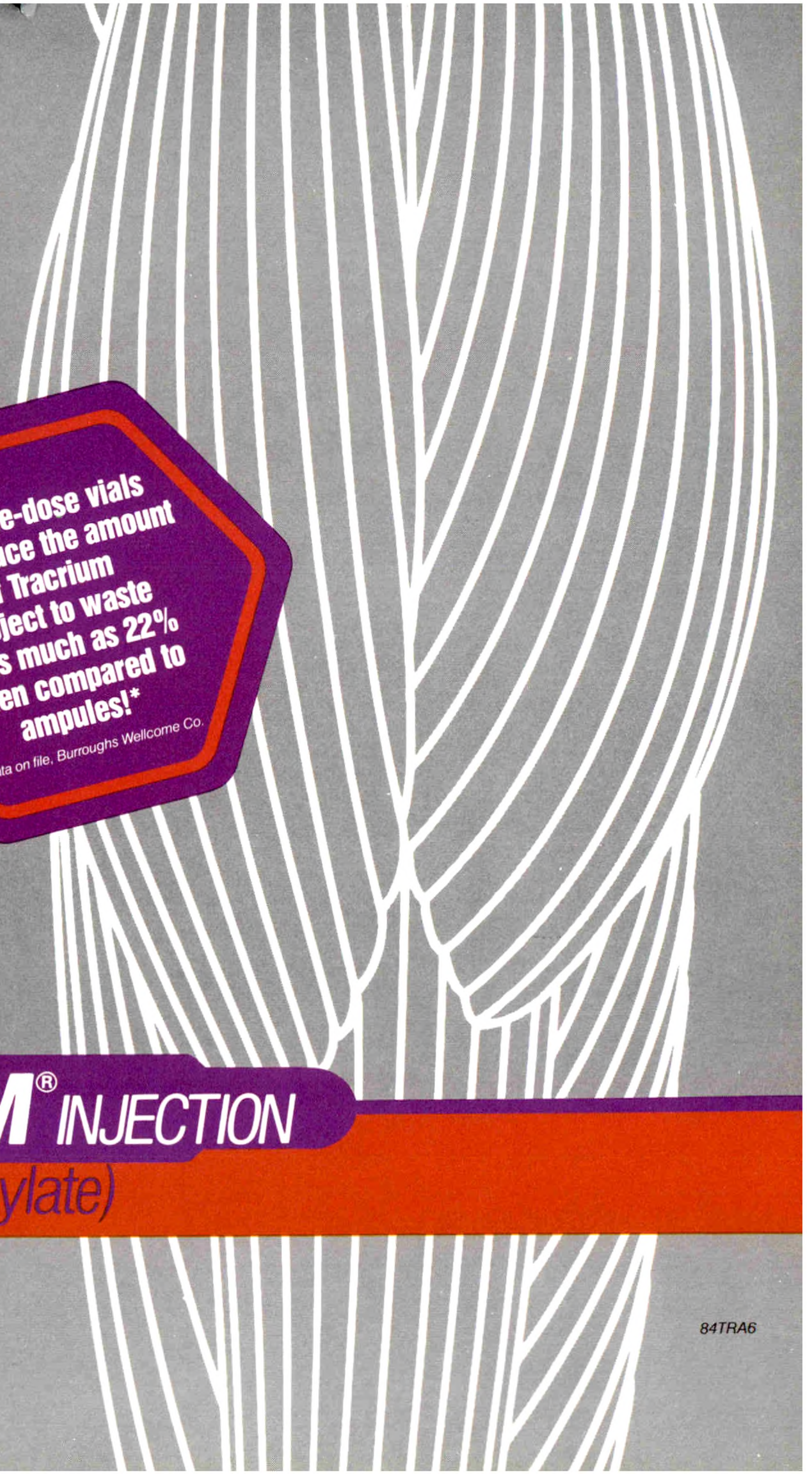
No mixing. Ready to use.

Good stability.

Tracrium is easily administered, requiring no premixing or measuring. At room temperature (25°C), potency loss is 5% per month.

Reference:
1. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine, abstracted. Anesthesiology 1982;57:A261.

Please see brief summary of prescribing information on following page.



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Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:
Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients with 0% change in heart rate. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequent reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Bolus Doses for Intubation and Maintenance of Neuromuscular Blockade:
Adults: A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular blockade generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Tracrium in these patients, and no specific dosage adjustments can be recommended. No Tracrium dosage adjustments are required for patients with renal disease.

Use by infusion: After administration of a recommended initial bolus dose of Tracrium (0.3 to 0.5 mg/kg), a diluted solution of Tracrium can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures. Infusion of Tracrium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of Tracrium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia.

The neuromuscular blocking effect of Tracrium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Tracrium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of Tracrium infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane. In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of Tracrium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of Tracrium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Tracrium infusion solutions may be prepared by admixing Tracrium Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Spontaneous degradation of Tracrium has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Tracrium for infusion.

The amount of infusion solution required per minute will depend upon the concentration of Tracrium in the infusion solution and the dose of Tracrium desired (see table).

Tracrium (atracurium besylate)—Rates of Infusion for Concentrations of 0.2 and 0.5 mg/ml

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (ml/kg/min)	
	0.2 mg/ml*	0.5 mg/ml**
5	0.025	0.010
6	0.030	0.012
7	0.035	0.014
8	0.040	0.016
9	0.045	0.018
10	0.050	0.020

*2 ml of 1% (10 mg/ml) Tracrium Injection added to 98 ml of diluent
**5 ml of 1% (10 mg/ml) Tracrium Injection added to 95 ml of diluent

U.S. Patent No. 4179507

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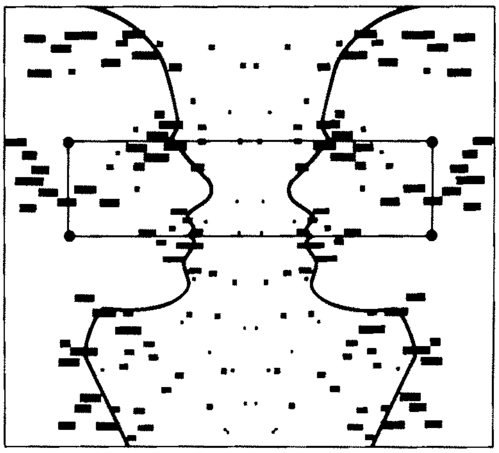

DOCUMED'87

Imaging and Visual Documentation in Medicine

MAY 24-27, 1987, RAI CONGRESS CENTRE, AMSTERDAM, THE NETHERLANDS

Medical Imaging and Visual Documentation techniques are becoming increasingly sophisticated, giving physicians invaluable diagnostic tools, for examining virtually every area of human physiology and pathology. But this growth in scope and scale makes it increasingly difficult for physicians to keep abreast of all the latest developments. In response to this clear and clearly expressed need, the International Society for Photoscopy is organizing DOCUMED EUROPE '87, the first European conference on imaging technology and visual documentation in medicine.

DOCUMED EUROPE '87 will be held at the RAI Congress Centre in Amsterdam, The Netherlands, from May 24-27, 1987.

A comprehensive range of topics will be covered in the plenary sessions and in minisymposia, seminars and workshops.

Running concurrently with the conference, VIDIMED '87 will be the first international exhibition devoted exclusively to the hardware and software of imaging technology and visual documentation in medicine.

For full details on participation in DOCUMED EUROPE '87, and VIDIMED '87 please contact:

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Europaplein 12, 1078 GZ Amsterdam, The Netherlands
Tel: (31)20-44 08 07, Telex: 13499 raico nl

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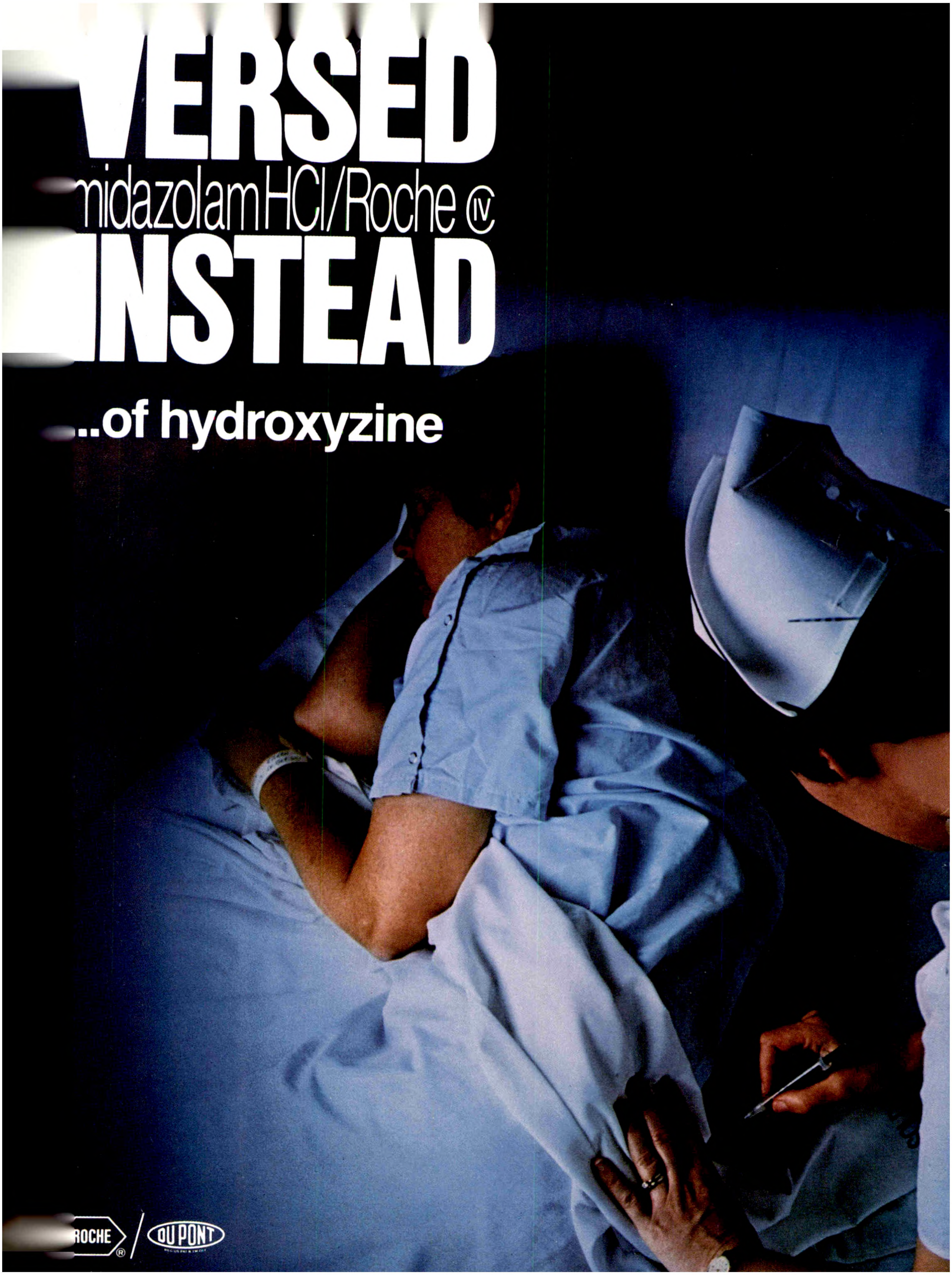

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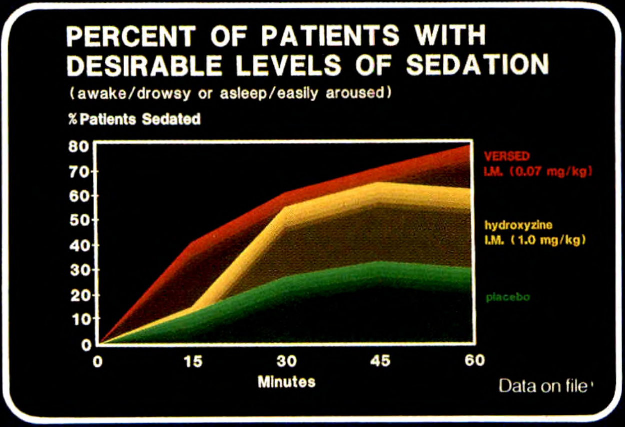

Data on file[1]

Desirable Level of Sedation at 15 minutes	VERSED	hydroxyzine
	43% (64/149)	19% (19/101)

• Virtually painless

Incidence of pain at I.M. injection site[2]

VERSED	hydroxyzine
alone 4.5% (12/269)	alone 47.1% (64/136)
with other agents 1.8% (2/111)	with other agents 62.7% (32/51)

• Pronounced amnestic effect

The maximum amnestic effect occurred between 30 and 60 minutes after VERSED (0.08 mg/kg) administration.[2]

Caution patients about driving or operating hazardous machinery after receiving VERSED.

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A significant advance in premedication

References: 1. Data on file (Doc. #069-001), Roche Laboratories. **2.** VERSED® (brand of midazolam HCl/Roche) Ⓒ, Scientific Summary, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, NJ.

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INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by 25% to 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) *IM use:* Inject deep in large muscle mass. *IV use:* Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.09% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

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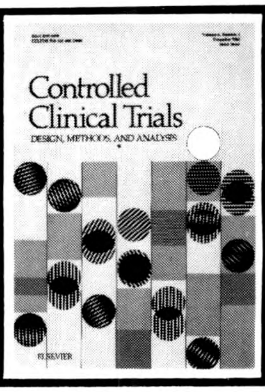

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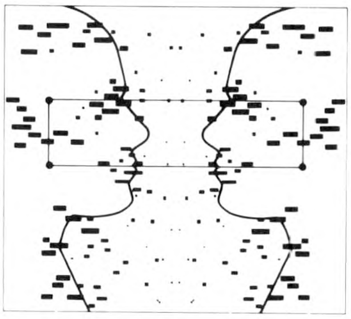

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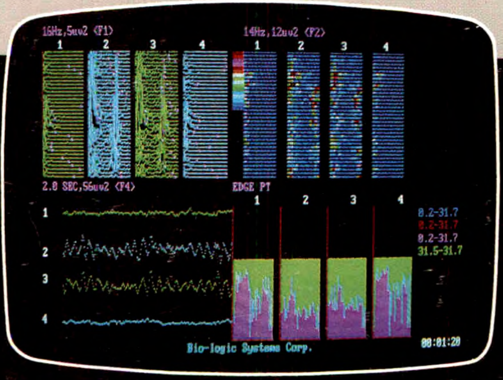

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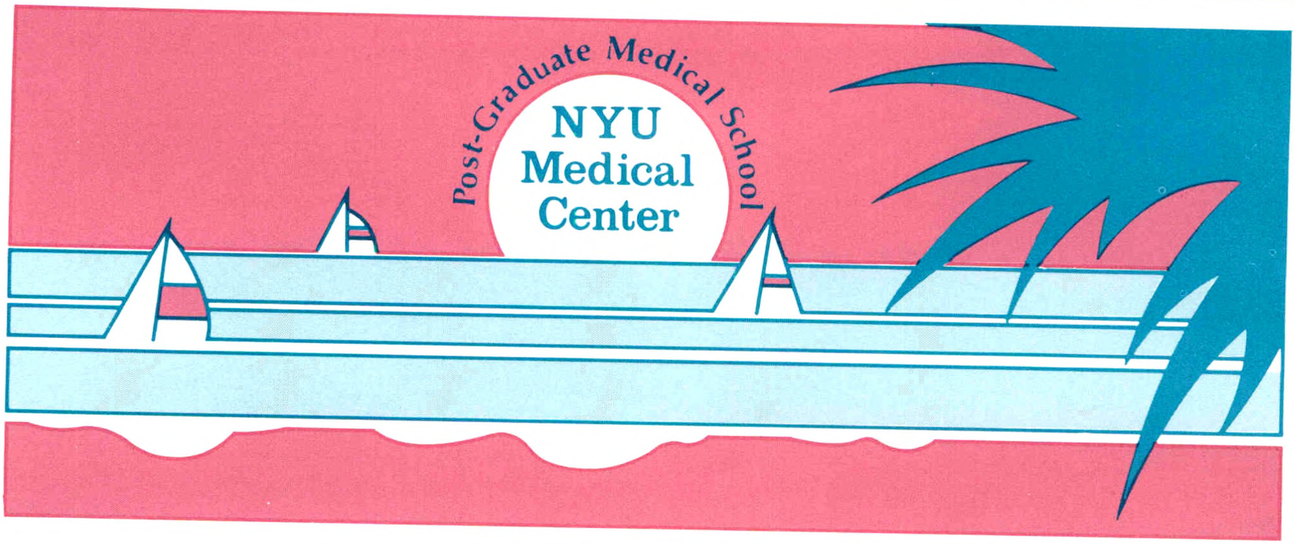

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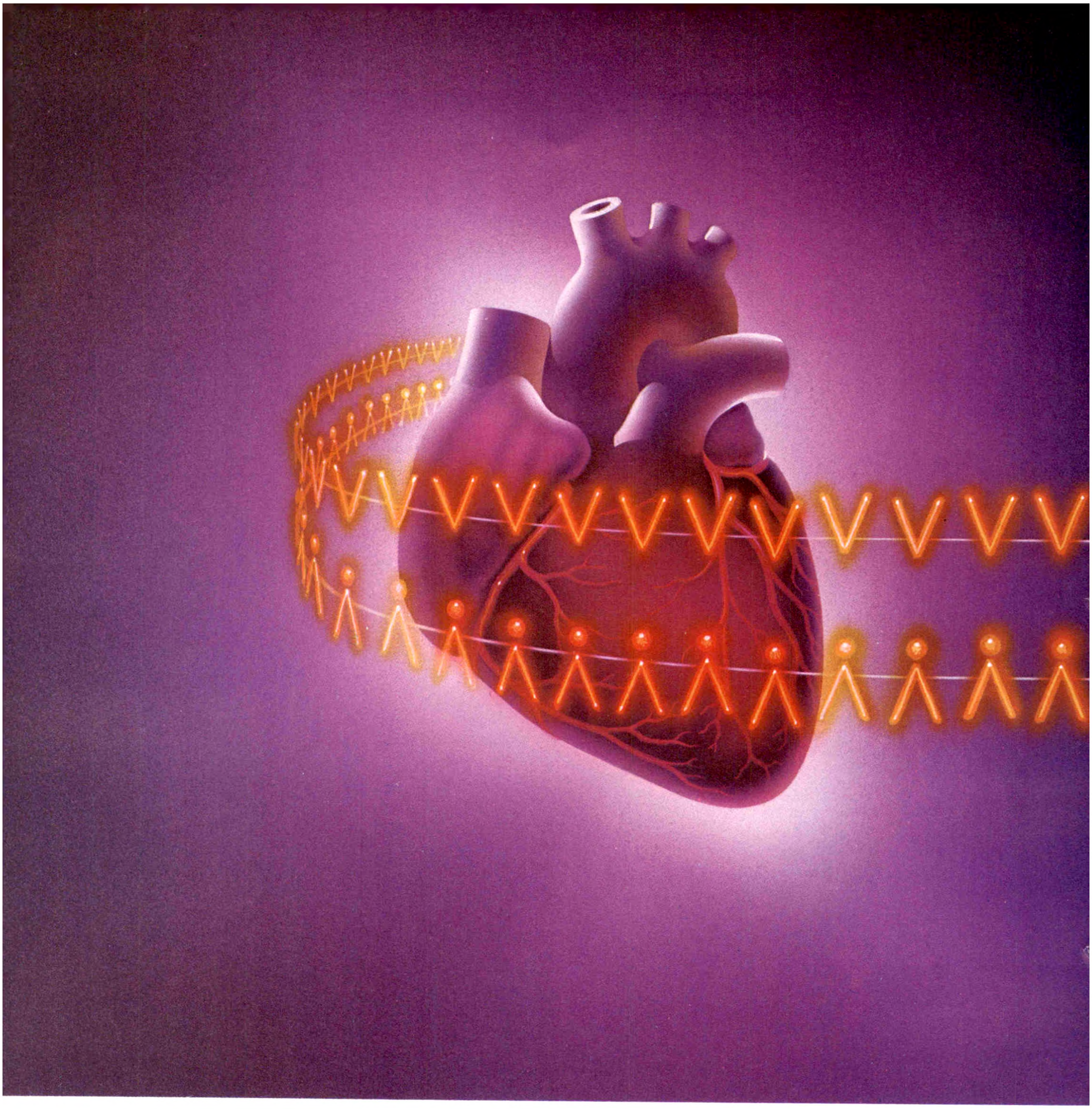

References: 1. Sanford TJ Jr, Smith NT, Dec-Silver H, et al: A comparison of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: Induction, emergence, and extubation. *Anesth Analg* 1986;65:259-266. 2. de Lange S, Boscoe MJ, Stanley TH, et al: Comparison of sufentanil-0_2 and fentanyl-0_2 for coronary artery surgery. *Anesthesiology* 1982;56:112-118. 3. Benefiel DJ, Roizen MF, Lampe GH, et al: Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia, abstracted. *Anesthesiology* 1986;65(3A):A516.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate)is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

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SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist actien, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease

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Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involv-

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

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These memberships are entered on a calendar year basis only.

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

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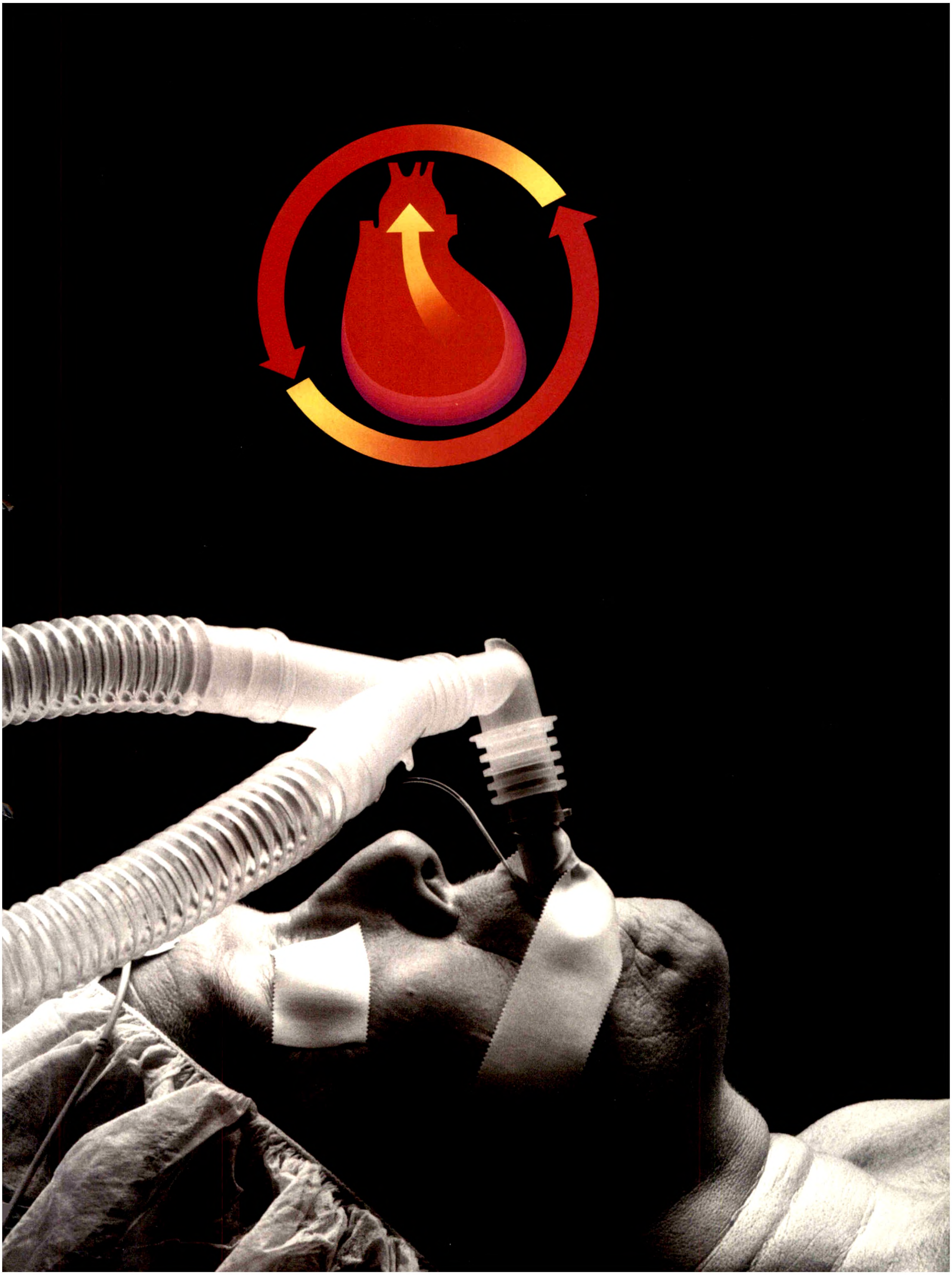

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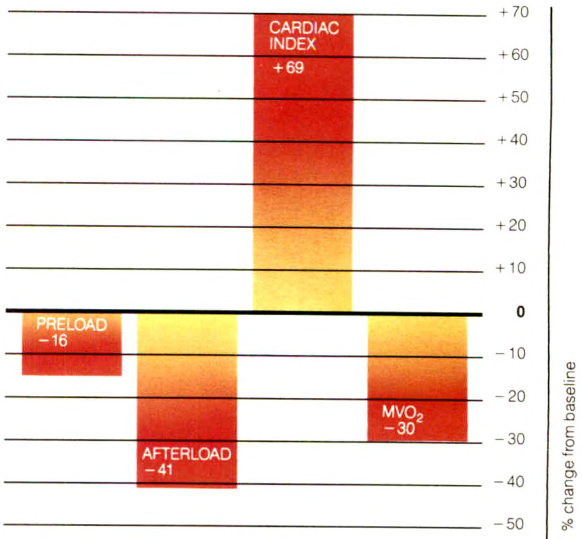

†n = 8. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.[1]

Please see last page for important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations.

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State-of-the-heart

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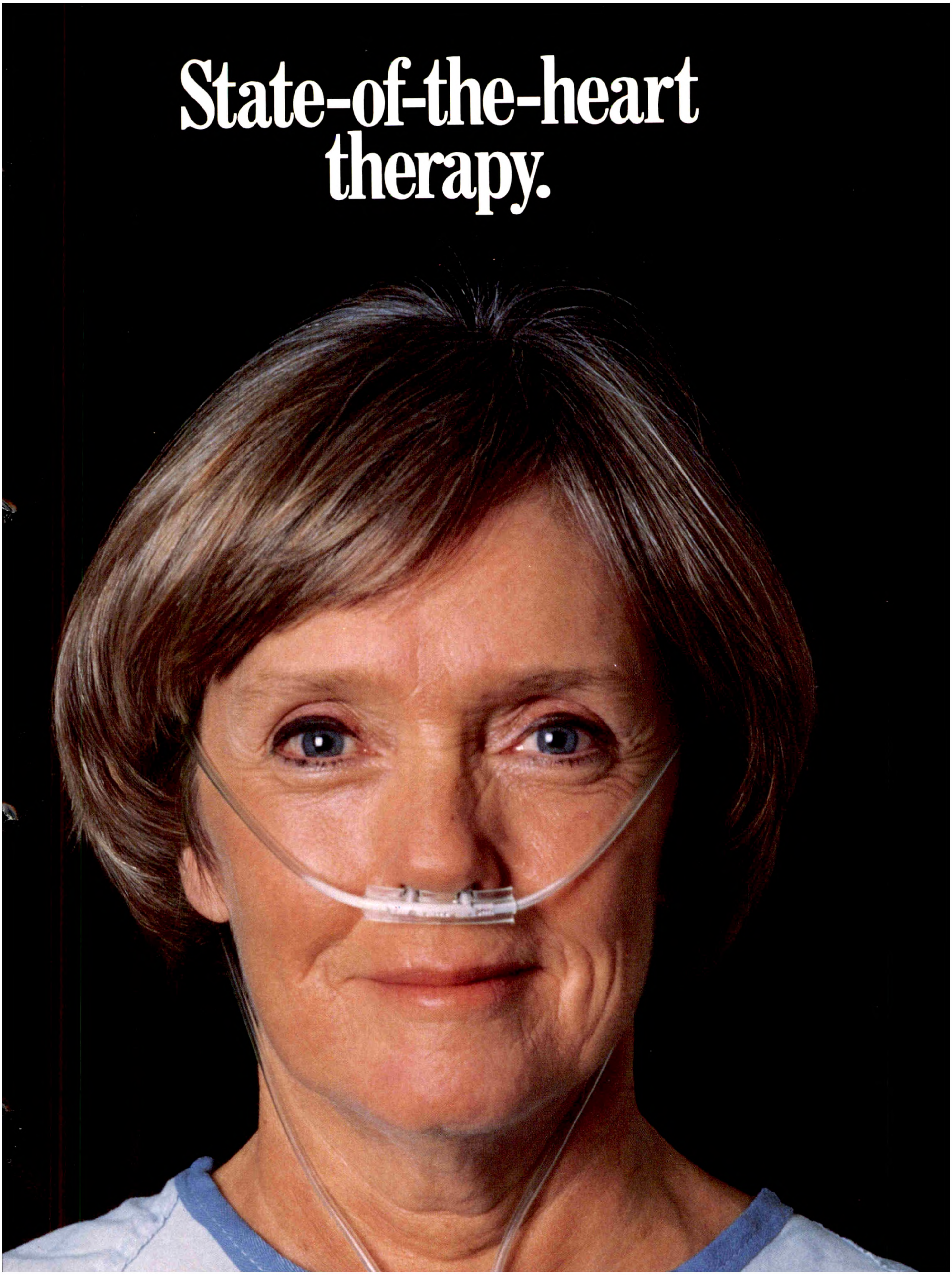
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INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General*: INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C*. In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is no certain, but possible hypersensitivity reactions should be considered in an patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site o injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but genera measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions*: Asymptomatic platelet count reduction (to less than 150,000/mm³) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm³ occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepato toxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersens tivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

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7 The Brachial Plexus
8 The Nerves Arising from the Brachial Plexus
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10 The Ulnar Nerve
11 The Radial Nerve
12 The Digital Nerves
13 The Cauda Equina, Lumbar and Sacral Nerve Roots, and Spinal Nerves

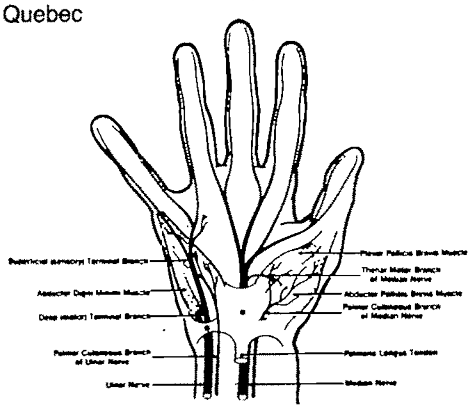
Superficial (sensory) Terminal Branch
Abductor Digiti Minimi Muscle
Deep (motor) Terminal Branch
Palmar Cutaneous Branch of Ulnar Nerve
Ulnar Nerve
Flexor Pollicis Brevis Muscle
Thenar Motor Branch of Median Nerve
Abductor Pollicis Brevis Muscle
Palmar Cutaneous Branch of Median Nerve
Palmaris Longus Tendon
Median Nerve

FIGURE 12.1 Palmar view of the right wrist and hand, showing the course and branching of the median and ulnar nerves. These nerves first divide into the common *digital nerves, which then divide further to become individual* proper *palmar digital nerves. The transverse carpal ligament and its extension, which forms the roof of Guyon's canal, are marked with asterisks.*

14 The Lumbosacral Plexus
15 The Sciatic Nerve, the Gluteal and Pudendal Nerves, and the Posterior Cutaneous Nerve of the Thigh
16 The Common Peroneal Nerve
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midazolam HCl/Roche ⓘⓥ
INSTEAD
...of thiopental

ROCHE® / DU PONT

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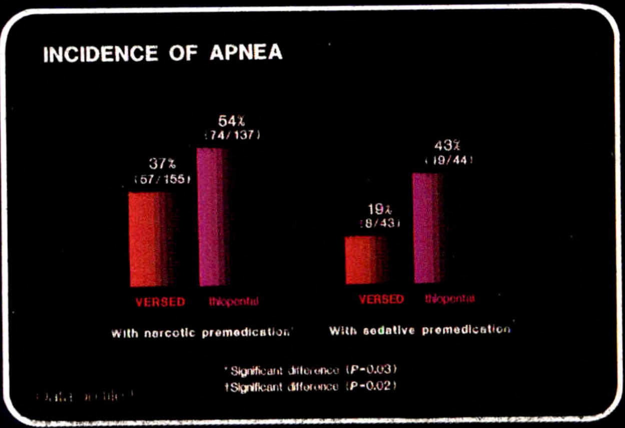
Key advantages in induction

• Significantly less apnea



• Better hemodynamic stability

While differences were not statistically significant, VERSED I.V. produced less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance…and a less pronounced increase in mean right atrial pressure[2]

• Pronounced anterograde amnesia

Significantly more VERSED-treated patients (24/24) had complete or partial anterograde amnesia than did thiopental-treated patients (13/26)[1]

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and familiar with all dosing and administration guidelines. Reduce dosage in elderly and debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve.

INJECTABLE

VERSED®

brand of
midazolam HCl Roche ⓒⅣ
equivalent to 5 mg/mL

A significant advance in anesthetic induction

References: 1. Data on file (Doc. #069-001, 004, 005, 007), Roche Laboratories. **2.** VERSED® (brand of midazolam HCl/Roche) Ⓒ, Scientific Summary, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, NJ, 1986.

VERSED®
(brand of midazolam HCl/Roche) Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by 25% to 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust

VERSED® (brand of midazolam HCl/Roche)

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) *IM use:* Inject deep in large muscle mass. *IV use:* Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.09% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

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Noel W. Lawson, MD, Chairman
62nd Congress Program Committee

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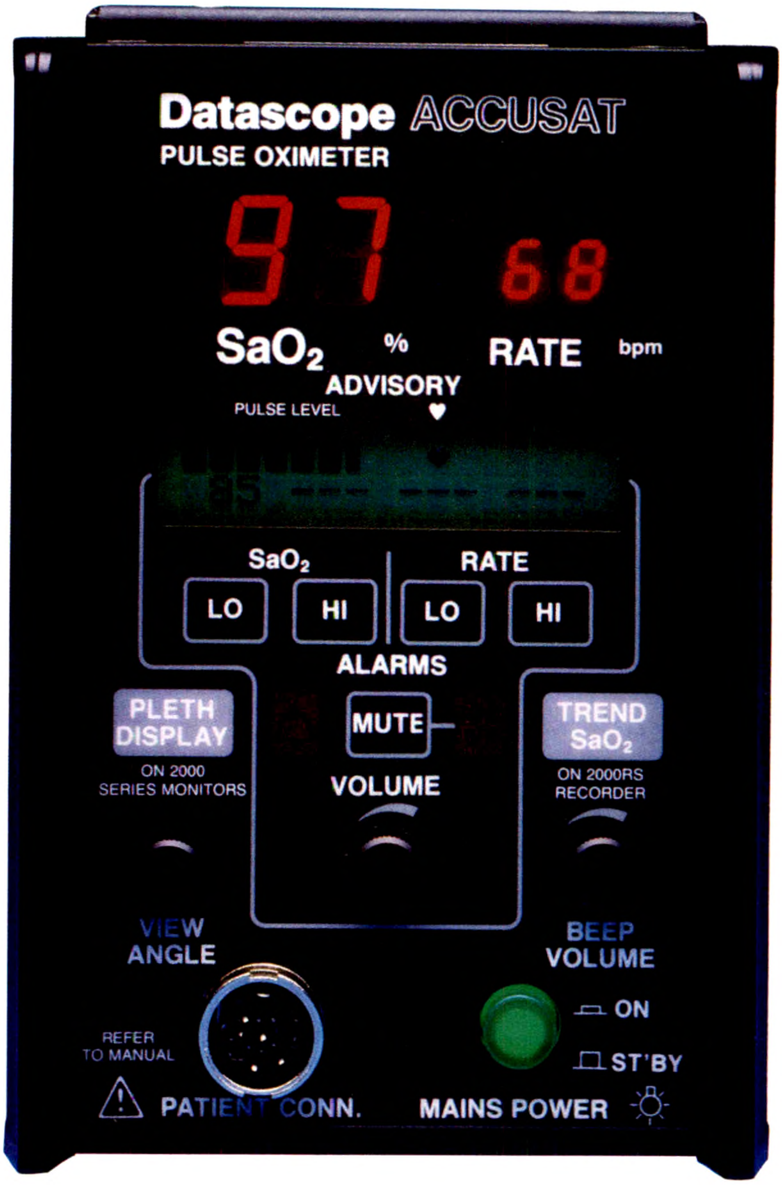

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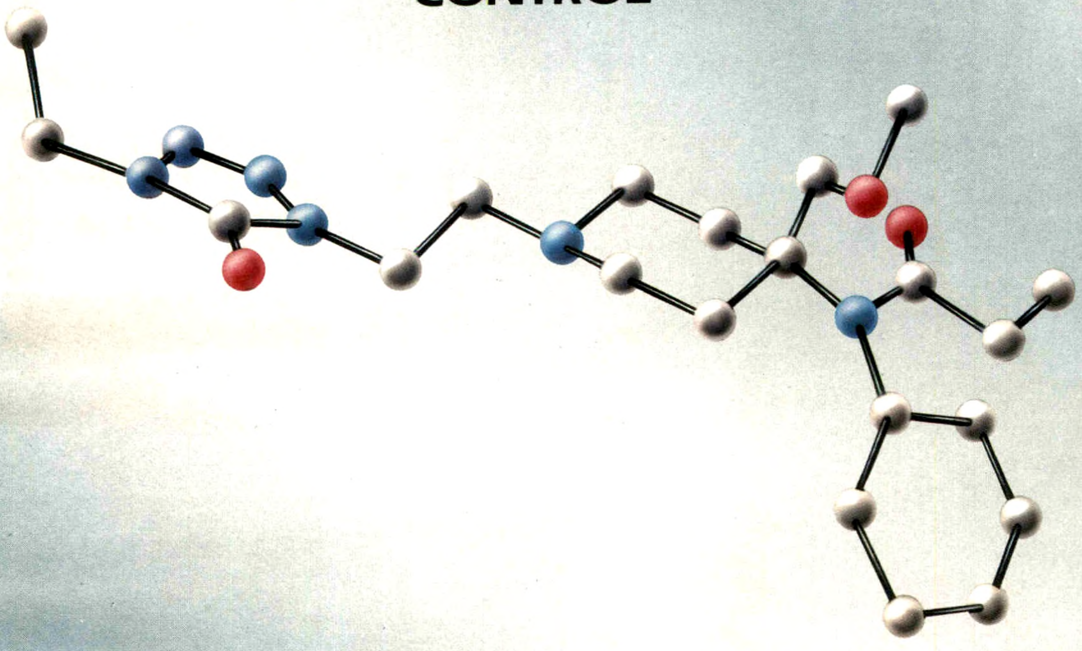

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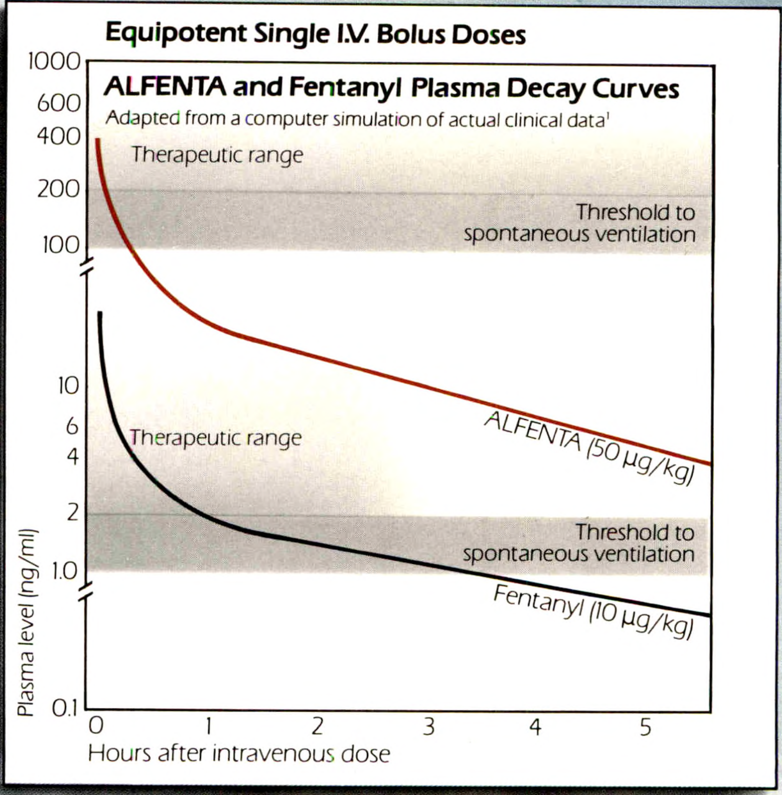

Equipotent Single I.V. Bolus Doses

ALFENTA and Fentanyl Plasma Decay Curves

Adapted from a computer simulation of actual clinical data[1]

Repeated or continuous administration of ALFENTA produces increasing plasma concentrations and an accumulation of the drug.

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RAPID ONSET

for prompt control of hemodynamic response to surgical stimulation*

*As with other opioids, hypotension and bradycardia have been reported.

ALFENTA 1.1 minute vs. fentanyl 6.4 minutes

Onset of opioid-induced sedation as measured by maximal electroencephalographic (EEG) changes following peak plasma levels, in a clinical study comparing ALFENTA infusion 1500 μg/min and fentanyl infusion 150 μg/min.[2] ALFENTA crosses the blood brain barrier faster because at body pH, 90% is unionized while 90% of fentanyl is ionized.

SHORT DURATION OF ANALGESIC ACTION

permits titrating to patient response

The smaller volume of distribution seen with ALFENTA results in higher plasma concentrations, making more of the drug available to the liver for elimination. This results in a significantly shorter terminal elimination half-life. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

*Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may produce more prolonged postoperative recovery.

Comparative Pharmacokinetics in Man
(mean values following single bolus injections)

	ALFENTA[3] (N=11)	Fentanyl[4] (N=7)
Distribution (t ½ π, min)	1.2	1.65
Redistribution (t ½α, min)	11.6	13.4
Elimination (t ½β, min)	94.0	219.0
Volume of Distribution (Vd, L/kg)	0.86	4.0
Plasma Clearance* (Cl, ml/kg/min)	6.4	12.6
Protein Binding[5]	92.1[5]	84.4[5]

PROMPT RECOVERY*

In short-stay (major, minor gynecologic) procedures

Five studies[6] of patients given a mean total dose of 9.3–62.2 μg/kg of ALFENTA over 10 to 60 minutes (mean duration) reveal the following:

Number of Patients	Time to Response† to Verbal Commands	Time† to Establish Alertness
167	**2 min** (0 to 44)	**4 min** (1 to 178)

*Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.
†Median time measured from discontinuance of nitrous oxide.

In longer (gynecologic, general) procedures using the infusion techniques: rapid return toward optimal function

Three studies[7] of patients given a mean loading dose of 45–71 μg/kg of ALFENTA, a mean infusion rate of 1.0–2.2 μg/kg/min with a mean duration of anesthesia 1.8 to 2.9 hours, reveal the following:

Number of Patients	Time† to Awake	Time† to Establish Alertness
71	**3 min** (– 5 to 59)	**13 min** (0 to 64)

Please see full Prescribing Information and references at the end of this advertisement.

RAPID-ACTING

Alfenta®

(alfentanil HCl) Injection CII

OFFERS A PHARMACOKINETIC PROFILE THAT PERMITS FLEXIBILITY OF DOSING TECHNIQUE

▲ **BOLUS/INCREMENTAL ADMINISTRATION**
for short procedures

▲ **CONTINUOUS INFUSION**
for general procedures

Each ampoule contains alfentanil HCl for intravenous use, **500 µg/ml** as base.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

Please see full Prescribing Information and references at the end of this advertisement.

ADULT DOSAGE GUID

BOLUS/INCREMENTAL ADMINISTRATI

For short procedures in spontaneously breathing patients:

An initial bolus loading dose of 8 to 20 µg/kg administered before barbiturate provides analgesic protection against hemodynamic response to surgical stress with rapid recovery. In very short, relatively unstressful procedures, additional doses are often unnecessary.

For procedures lasting 30 to 60 minutes:

An initial bolus loading dose of 20 to 50 µg/k ALFENTA, administered before thiopental, provides an analgesic level sufficient to reduce the hemodynamic response to laryngoscopy intubation. Additional small increments, given needed, permit titrating to patient response.

CONTINUOUS INFUSION

For procedures lasting more than 45 minutes:

A preintubation loading dose of 50 to 75 µg/k administered over 30 to 90 seconds before thiopental, provides an analgesic level sufficien to attenuate the hemodynamic response to intubation and incision.

An average infusion rate of 1 to 1.5 µg/kg/mi has been shown to provide adequate analge reduce sympathetic response to surgical stress, and provide rapid recovery with some postoperative analgesia. Changes in vital signs may generally be controlled by increasing the infusion rate and/or administration of a bolus dose of ALFENTA 7 µg/kg.

pprox. Duration f Anesthesia	Initial Dose	Maintenance Dose	Total Dose
≤30 MIN LFENTA administered y incremental injection, vith N_2O/O_2 atient spontaneously reathing, r ssisted ventilation vhen required	**8-20 µg/kg** over a one- to two-min period (based on expected duration)	**3-5 µg/kg given incrementally** or **0.5-1 µg/kg/min by continuous infusion** ▲ Titrate dose to patient's respiratory response ▲ In clinical studies, maintenance doses were seldom required in cases with a duration of anesthesia of about 10 min	**8-40 µg/kg** ▲ In clinical studies, a mean total dose of approximately 30 µg/kg was required for cases of approximately 30-min duration
30-60 MIN LFENTA administered incremental injection, vith N_2O/O_2 ssisted or controlled ventilation required	**20-50 µg/kg** (based on expected duration)	**5-15 µg/kg** ▲ Clinical studies have indicated that a bolus dose of approximately 7 µg/kg may be administered to control increases in blood pressure or heart rate ▲ When responses were not controlled or recurred in these studies, up to two additional bolus doses of approximately 7 µg/kg were given over five min	**Up to 75 µg/kg**
>45 MIN LFENTA administered y continuous infusion, vith N_2O/O_2 ssisted or controlled entilation required	**50-75 µg/kg**	**0.5-3.0 µg/kg/min by continuous infusion** ▲ Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the infusion rate up to a maximum of 4 µg/kg/min and/or administration of bolus doses of 7 µg/kg. If changes are not controlled after three bolus doses given over a five min period, a barbiturate, vasodilator, and/or inhalation agent should be used ▲ In absence of signs of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation ▲ Infusion should be discontinued at least 10 to 15 min prior to the end of surgery ▲ An average ALFENTA infusion rate of 1 to 1.5 µg/kg/min has been shown to maintain hemodynamic stability, dampen sympathetic response to surgical stress and to provide rapid recovery with some postoperative analgesia ▲ Within the last 15 min of surgery, administration of approximately 7 µg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered rather than increasing infusion rate in response to signs of lightening anesthesia	Dependent on duration of procedure

Alfenta®

(alfentanil HCl) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

ALFENTA (alfentanil hydrochloride) Injection is an opioid analgesic chemically designated as N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride (1:1) with a molecular weight of 452.98. ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CLINICAL PHARMACOLOGY

ALFENTA (alfentanil hydrochloride) is an opioid analgesic with a rapid onset of action.

At doses of 8-40 μg/kg for surgical procedures lasting up to 30 minutes, ALFENTA provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equipotent fentanyl dosages. For longer procedures, doses of up to 75 μg/kg attenuate hemodynamic responses to laryngoscopy, intubation and incision, with recovery time comparable to fentanyl. At doses of 50-75 μg/kg followed by a continuous infusion of 0.5-3.0 μg/kg/min, ALFENTA attenuates the catecholamine response with more rapid recovery and reduced need for postoperative analgesics as compared to patients administered enflurane. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

The pharmacokinetics of ALFENTA as determined in 11 patients given single bolus injections of 50 or 125 μg/kg, can be described as a three-compartment model; distribution half-life ranged from 0.4-3.1 minutes; redistribution half-life ranged from 4.6-21.6 minutes; and terminal elimination half-life ranged from 64.1-129.3 minutes (as compared to a terminal elimination half-life of approximately 219 minutes for fentanyl and approximately 164 minutes for sufentanil). Linear kinetics have been described only with plasma concentrations up to 1000 ng/ml. Repeated or continuous administration of ALFENTA produces increasing plasma concentration and an accumulation of the drug, particularly in patients with reduced plasma clearance. The liver is the major site of biotransformation.

ALFENTA has an apparent volume of distribution of 0.6-1.0 L/kg, which is approximately one-fourth that of fentanyl, with a plasma clearance range of 1.7-17.6 ml/kg/min as compared to approximately 12.6 ml/kg/min for fentanyl.

Approximately 81% of the administered dose is excreted within 24 hours and only 0.2% of the dose is eliminated as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of ALFENTA is approximately 92%.

In one study involving 15 patients administered ALFENTA with nitrous oxide/oxygen, a narrow range of plasma ALFENTA concentrations, approximately 310-340 ng/ml, was shown to provide adequate anesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anesthesia for superficial surgery.

ALFENTA has an immediate onset of action. At dosages of approximately 105 μg/kg, ALFENTA produces hypnosis as determined by EEG patterns; an anesthetic ED_{90} of 182 μg/kg for ALFENTA in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 μg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 μg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-intubation loading dose of 50-75 μg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of ALFENTA infusion administered at a rate of 0.5-3.0 μg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anesthetics were reduced by thirty to fifty percent during the first 60 minutes of maintenance in patients administered anesthetic doses (above 130 μg/kg) of ALFENTA as compared to patients given doses of 4-5 mg/kg thiopental for anesthetic induction. At anesthetic induction dosages, ALFENTA provides a deep level of anesthesia during the first hour of anesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anesthetic induction dose of ALFENTA, requirements for ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may prolong postoperative recovery.

Bradycardia may be seen in patients administered ALFENTA. The incidence and degree of bradycardia may be more pronounced when ALFENTA is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of ALFENTA has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged.

Patients administered doses up to 200 μg/kg of ALFENTA have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Muscular rigidity will occur with an immediate onset following anesthetic induction dosages. Preventative measures (see WARNINGS) may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

INDICATIONS AND USAGE

ALFENTA (alfentanil hydrochloride) is indicated:

as an analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen.

as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.

as a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF ALFENTA.

CONTRAINDICATIONS

WARNINGS

ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS

The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE

ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION

The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See Dosage Chart for the use of ALFENTA: 1) by incremental injection as an analgesic adjunct to anesthesia with barbiturate / nitrous oxide / oxygen for short surgical procedures (expected duration of less than one hour); 2) by continuous infusion as a maintenance analgesic with nitrous oxide / oxygen for general surgical procedures; and 3) by intravenous injection in anesthetic doses for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 minutes.

Usage in Children: Clinical data to support the use of ALFENTA in patients under 12 years of age are not presently available. Therefore, such use is not recommended.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections).

In patients administered anesthetic (induction) dosages of ALFENTA, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of ALFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

The physical and chemical compatibility of ALFENTA have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of ALFENTA infusion have been conducted with ALFENTA diluted to a concentration range of 25 μg/ml to 80 μg/ml.

As an example of the preparation of ALFENTA for infusion, 20 ml of ALFENTA added to 230 ml of diluent provides a 40 μg/ml solution of ALFENTA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DOSAGE RANGE CHART

Indication	Incremental Injection	Incremental Injection	Continuous Infusion*	Anesthetic Induction
Approximate Duration of Anesthesia	≤ 30 mins	30-60 mins	> 45 mins	> 45 mins
Induction Period (Initial Dose)	8-20 μg/kg	20-50 μg/kg	50-75 μg/kg	130-245 μg/kg
Maintenance Period (Increments/ Infusion)	3-5 μg/kg or 0.5-1 μg/kg/min	5-15 μg/kg	0.5-3.0 μg/kg/min Average Infusion Rate 1-1.5 μg/kg/min	0.5 to 1.5 μg/kg/min or general anesthetic
Total Dose	8-40 μg/kg	up to 75 μg/kg	dependent on duration of procedure	dependent on duration of procedure
Effects	Spontaneously breathing or assisted ventilation when required.	Assisted or controlled ventilation required. Attenuation of response to laryngoscopy and intubation.	Assisted or controlled ventilation required. Some attenuation of response to intubation and incision, with intraoperative stability.	Assisted or controlled ventilation required. Administer slowly (over three minutes). Concentration of inhalation agents reduced by 30-50% for initial hour.

INFUSION DOSAGE

***Continuous Infusion:** 0.5-3.0 μg/kg/min administered with nitrous oxide / oxygen in patients undergoing general surgery. Following an anesthetic induction dose of ALFENTA, infusion rate requirements are reduced by 30-50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the rate up to a maximum of 4.0 μg/kg/min and/or administration of bolus doses of 7 μg/kg. If changes are not controlled after three bolus doses given over a five minute period, a barbiturate, vasodilator, and/or inhalation agent should be used. Infusion rates should always be adjusted downward in the absence of these signs until there is some response to surgical stimulation.

Rather than an increase in infusion rate, 7 μg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered in response to signs of lightening of anesthesia within the last 15 minutes of surgery. Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

HOW SUPPLIED

Each ml of ALFENTA (alfentanil hydrochloride) Injection for intravenous use contains alfentanil hydrochloride equivalent to 500 μg of alfentanil base. ALFENTA Injection is available as:

NDC 50458-060-02, 2 ml ampoules in packages of 10
NDC 50458-060-05, 5 ml ampoules in packages of 10
NDC 50458-060-10, 10 ml ampoules in packages of 5
NDC 50458-060-20, 20 ml ampoules in packages of 5

Protect from light. Store at room temperature 15°-30°C (59°-86°F).
U.S. Patent No. 4,167,574 March 1987 49-7619901-M

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, NJ 08854

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- ▲ **As with other opioids, bradycardia and hypotension have been reported**
- ▲ **Offers moment-to-moment control with bolus or incremental injection—or continuous infusion**
- ▲ **Generally rapid recovery**
- ▲ **Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained**
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JPI-579

Isoflurane Has a Greater Margin of Safety than Halothane in Swine with and without Major Surgery or Critical Coronary Stenosis

Sandra L. Roberts, MD, Mads Gilbert, MD, and John H. Tinker, MD

Roberts SL, Gilbert M, Tinker JT. Isoflurane has a greater margin of safety than halothane in swine with and without major surgery or critical coronary stenosis. Anesth Analg 1987;66:485–91.

The fatal/anesthetic ratio (FAR) in 44 swine weighing 32.6 ± 0.7 kg (SEM) was determined. Fatal anesthetic concentration (the numerator for FAR) was defined as the end-tidal concentration at which the pig lived at least 10 min, during experiments that involved step increments in anesthetic concentrations. Previously reported MAC was used as the "anesthetic" concentration (denominator) to determine FAR. Halothane was compared to isoflurane and the question of whether major surgery might reduce FAR was investigated. The major surgery groups included one open chest group with each volatile anesthetic studied during coronary reserve measurements, and two groups that had LAD critical coronary stenoses. Thus volatile agents were compared with vs without major surgery, and with vs without a critical coronary stenosis. The FAR for isoflurane was approximately double that of halothane. Further, addition of major surgery did not produce significant deterioration in FAR with isoflurane. In contrast, with halothane there was a significant (approximately 20%) decrease in FAR, despite values already only half that seen with isoflurane, when major surgery was added. Presence of a critical coronary stenosis was not associated with a worsened FAR for isoflurane or halothane. It was concluded that the fatal/anesthetic ratio for isoflurane in pigs is 1.9 times greater than that for halothane. Addition of major surgery did not affect FAR when isoflurane was the anesthetic but did when halothane was used. Critical coronary stenosis did not worsen FAR. Because these results are nearly identical with those reported previously in small mammals, the doubled safety margin seen with isoflurane may have clinical relevance.

Key Words: ANESTHETICS, VOLATILE—isoflurane, halothane. HEART—coronary stenosis.

Drug safety margins are easy to determine if there is a well defined drug effect and easily quantitated toxicity. If this is the case, the toxic therapeutic ratio is a standard way of assessing the drug's safety margin. For volatile anesthetics, there is no specific therapeutic effect, nor is there a predictable marker for onset of toxicity. Previous attempts to quantify anesthetic safety margins have chosen apnea (1), respiratory failure (2,3), cardiac failure (2,3), and LD_{50} (4) as "toxic" end points and compared them to previously published MAC levels (1), loss of righting reflex (4), loss of individual tail clamp response (2,3), and prevention of movement and heart rate response to other noxious stimuli (4). We utilized fatal anesthetic concentration divided by the 1 MAC level (fatal/anesthetic ratio, FAR). By using a fatal end point, we deliberately eliminated questions of *when* toxicity might begin as well as how far anesthetic dose can be increased before toxicity becomes irreversible. Previous studies of toxicity of volatile anesthetics (2–4) have utilized small animals, except for one study on dogs (1). No study has compared anesthesia without vs with superimposed surgical stress, a point of obvious relevance to clinical practice.

Because addition of surgery to anesthesia is associated with a wide variety of autonomic and hormonal responses, many of which affect cardiac function, we hypothesized that addition of major surgery would significantly worsen the animal's tolerance for the agent, that is, it would affect FAR negatively. Myocardial ischemia has been reported to worsen when halothane is used in the presence of coronary stenosis (5–7). Accordingly, we reasoned that first adding major surgery alone and then adding a critical coronary stenosis to the major surgery in different groups, using a large mammal, might best mimic the clinical situations wherein any added or differential toxicity of volatile agents might be most important. Therefore,

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Table 1. Summary of Surgical Preparation, End-tidal Concentrations ([Et]) at MAC, and Death and FAR Values

Group	Agent	Surgical preparation	Open chest	n	MAC[Et][a]	Fatal[Et]	FAR[b]
H_1	Halothane	General preparation[c]	No	7	1.27 ± 0.03	2.46 ± 0.15	1.98 ± 0.06
H_2	Halothane	General prep, critical LAD stenosis	Yes	7	1.25 ± 0.03	2.10 ± 0.31	1.66 ± 0.21
H_3	Halothane	General prep, coronary reserve measurement	Yes	7	1.26 ± 0.04	2.06 ± 0.31	1.64 ± 0.24
H_4	Halothane	General prep, aortic snare, coronary reserve measurement	Yes	7	1.26 ± 0.03	1.84 ± 0.33	1.44 ± 0.27
I_1	Isoflurane	General preparation[c]	No	3	1.44 ± 0.01	4.90 ± 0.53	3.43 ± 0.38
I_2	Isoflurane	General prep, critical LAD stenosis	Yes	6	1.49 ± 0.07	3.02 ± 0.55	2.89 ± 0.61
I_3	Isoflurane	General prep, coronary reserve measurement	Yes	7	1.45 ± 0.02	4.41 ± 0.81	3.05 ± 0.55

All values are mean ± SD.

[a] MAC halothane = [Et] 1.25%, [Et] isoflurane 1.45%.

[b] FAR, fatal-anesthetic ratio. Values are group averages of *individual* FARs (mean ± SD).

[c] Tracheotomy, monitoring lines (see text).

our strategy was to compare fatal/anesthestic ratios during anesthesia with increments of halothane vs isoflurane 1) in the presence vs absence of major surgery; 2) with vs without addition of a critical coronary artery stenosis in a large mammal. We found isoflurane to be consistently associated with significantly better safety margins.

Methods

Data from a total of 44 separate animal experiments are reported herein. Using this protocol and some of these same animals we simultaneously completed two separate studies: 1) a study of comparative hemodynamic changes in animals with vs without critical coronary stenoses, (n = 13) and; 2) a study of coronary reactive hyperemia as an estimate of coronary reserve (n = 21). Both studies required major surgery and were designed using graded increments of volatile anesthetics with sufficient time to equilibrate at each MAC multiple level (see later). To these groups we added a third group of pigs (n = 10) studied in identical fashion with respect to graded agent level increments, but without major surgery.

General Preparation

In all groups, pigs weighing 26–37 kg were deprived of food but not water for 12 hr before experiments. Anesthesia was induced without premedication with only the agent under study (halothane n = 28, isoflurane n = 16) in oxygen using a large animal anesthesia mask. A catheter was placed in an ear vein for administration of muscle relaxant and maintenance fluids. After paralysis with succinylcholine and tracheal intubation via tracheotomy, the animals were ventilated to $Pa\text{CO}_2$ of 37 ± 2 mm Hg (± SEM). Arterial pressure (AP) was transduced via the right common carotid artery reached through the tracheotomy incision. Pulmonary artery pressures (PAP) and thermodilution cardiac outputs (CO) were measured via a 7F pulmonary artery catheter inserted through the femoral vein. AP, PAP, and ECG were continuously displayed and recorded. Cardiac output was measured in triplicate at each data point using iced 5% dextrose-water. Arterial blood gas tensions and pH values were frequently measured and rectal temperature maintained within 38 ± 0.5°C by means of warming blanket and heat lamp. Concentration of volatile agent under study was measured with a calibrated mass spectrometer (Perkin-Elmer) in gas continuously sampled from the endotracheal tube. Surgery was performed at approximately 1 MAC end-tidal [Et] concentration. For 1 MAC levels, we used 1.45% for isoflurane (8), and 1.25% for halothane (9).

Specific Animal Preparation

Table 1 presents each group's preparation and identification.

Controls (n = 10, groups H_1 and I_1). Animals in this group were not exposed to surgery apart from that required by the general preparation described earlier. These animals were done after the surgical groups. The length of agent exposure at each MAC level was the same as the average time spent in the surgical groups for each agent.

Critical coronary stenosis (n = 13, groups H_2 and I_2). After induction and placement of monitoring catheters, the pericardium was exposed through a median sternotomy and a cradle was formed. The shortest possible part of the left anterior descending coronary artery (LAD) was dissected to allow placement of a glycerine-filled hydraulic occluder and an oiled silk

Table 2. Number of Survivors at Each MAC Level

Group	0.5	1.0	1.25	1.50	1.75	2.0	2.5	3.0	3.5	4.0	4.5
H_1 closed	7	7	7	7	7	6	0	—	—	—	—
H_2 critical st	7	7	7	6	4	1	0	—	—	—	—
H_3 coronary res	7	7	7	6	4	1	0	—	—	—	—
H_4 BP control	7	7	6	5	2	0	—	—	—	—	—
F_1 closed	3	3	3	3	3	3	3	2	0	—	—
F_2 critical st	6	6	6	6	6	6	6	4	3	0	—
F_3 coronary res	7	7	7	7	7	7	7	5	2	1	0

suture. Distal LAD blood flow velocity was measured with a 20 mHz piezoelectric ultrasonic Doppler probe attached epicardially to the LAD with vacuum. By gradually expanding the occluder with glycerine via a micrometer syringe, we considered that a critical LAD stenosis had been established at the point where 10 sec total occlusion caused no reactive hyperemia upon release. This has been considered to occur with a stenosis such that distal coronary vasculature is maximally dilated (10). Placement of such critical LAD stenosis was performed at 1 MAC_{agent} before starting the protocol.

Coronary reactive hyperemia (*n* = 21, groups H_3, H_4, and I_3). After general preparation, a median sternotomy was performed and the heart was suspended in a pericardial cradle. Dissection was limited to the shortest possible proximal LAD segment needed to pass an oiled silk suture rigged as a snare through a thin tubing. No hydraulic occluder was employed. A 20 mHz Doppler probe adjacently attached with vacuum epicardially on the LAD served to measure coronary flow velocity. The snare allowed rapid on-off total LAD occlusions and was used for experiments designed to study coronary reserve. Three separate hyperemic responses, each provoked by 15 sec total flow arrest, were used to measure coronary reserve, flow repayment, and duration of reactive hyperemia (11) at each increment of $[Et]_{agent}$. Each of these animals was thus exposed to the stress of intermittent brief myocardial ischemia at least three times at each concentration level of agent tested. Hyperemic responses were not repeated until coronary blood flow returned to normal or until 3 min had passed. One of these groups using halothane (group H_4) had a snare placed around the aorta just distal to the left subclavian artery. The snare was used to mechanically elevate arterial blood pressure to the level previously recorded with isoflurane (group I_3) at each MAC level before reactive hyperemia in triplicate was tested. Except for groups H_1 and I_1, these animals were all part of studies designed for other purposes as well as FAR determination. The increments of increases in anesthetic concentrations, all the way to death, were identical. This provides the rationale for the fatal/anesthestic ratios reported here as one large group.

Calculation of Fatal/Anesthetic Ratio

We chose to use the reported MAC level of study agent (goals $MAC_{halothane}$ = 1.25%[Et], $MAC_{isoflurane}$ = 1.45%[Et]) as denominators when calculating individual fatal-anesthetic ratios rather than individually determined MACs, because of the possibility of time-related deterioration of the preparation. Fatal-anesthetic ratio (FAR) was therefore calculated as fatal [Et] divided by the 1 MAC level [Et] actually achieved in that animal. The fatal end-point was taken as the time at which transduced arterial pressure waves and visual cardiac function were no longer detectable.

Protocol for Fatal/Anesthetic Ratio Studies

Individual fatal/anesthetic ratios of halothane or isoflurane were established by exposure of each animal to step increments of one study agent until the death of each animal. $[Et]_{agent}$ was measured with a calibrated mass spectrometer. Care was taken to reach protocol MAC multiples with precision.

All groups were exposed to identical increments in $[Et]_{agent}$ regardless of their inclusion in other studies. Surgery was performed at 1 MAC. No anesthetic other than the study agent, and no other drugs except succinylcholine were given during each experiment. After completion of surgery, graded increments of MAC were achieved at the following levels: 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0 MAC, followed by 0.5 MAC steps until each animal died (Table 2). At least 15 min of stable $[Et]_{agent}$ was allowed at each level before recordings, but if the animal survived 10 min steady state $[Et]_{agent}$, that concentration was taken to be the fatal level. If the animal lived less than 10 min after achievement of a target $[Et]_{agent}$, then the fatal concentration was taken as the previous one. Each animal

Table 3. *P* Values for Comparisons between Groups

Contrasts	*P* value
Isoflurane vs halothane	0.0000[a]
Closed chest; isoflurane vs halothane	0.0010[a]
Open chest; isoflurane vs. halothane	0.0000[a]
Critical coronary stenosis; isoflurane vs halothane	0.0001[a]
Isoflurane closed chest vs open chest	0.2495
Isoflurane closed chest vs open chest	0.3746
Isoflurane closed chest vs critical coronary stenosis	0.2152
Isoflurane open chest vs critical coronary stenosis	0.6304
Halothane closed chest vs open chest	0.0000[a]
Halothane closed chest vs open chest	0.0026[a]
Halothane closed chest vs critical coronary stenosis	0.0000[a]
Halothane closed chest vs pressure controlled	0.0000[a]
Halothane open chest vs pressure controlled	0.1718
Halothane open chest vs critical stenosis	0.8807

[a] *P* values for group comparisons significant at the 0.0033 level. Determined by Bonferroni adjustment of overall significance value $P < 0.05$. Analysis by Satterthwaite approximation (*t*-test with modified degrees of freedom).

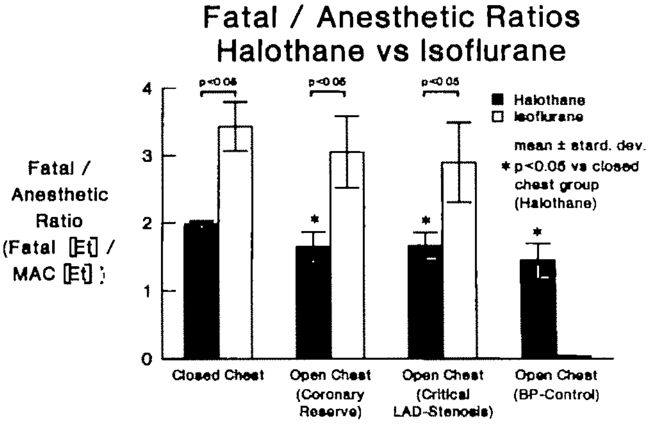

Figure 1. Fatal/anesthetic ratios of halothane vs isoflurane. Isoflurane's fatal/anesthetic ratio significantly exceeds halothane's for each comparison indicated by brackets. Asterix indicates a significant difference between each surgical group and closed chest group with halothane.

in all other groups was exposed to the agent studied for a period of time at each MAC step nearly identical to the average exposure at each step in groups H_3 and I_3, because these groups required the most time to complete the experiments after achievement of target state $[Et]_{agent}$. Care was taken not to overshoot agent concentrations at each MAC level.

Statistical Analyses

Data presented are mean ± SD. Data analysis used the Satterthwaite approximation (12,13) (*t*-test with modified degrees of freedom). Because of differences in variance between isoflurane groups and halothane groups, use of tests that assume homogeneous variance would have been inappropriate. The Satterthwaite approximation does not assume uniform variance. Comparisons were made with Bonferroni adjustments to protect the overall error rate of 0.05. $P < 0.05$ was considered significant.

Results

End-tidal [Et] at MAC at death as well as the calculated fatal/anesthetic ratios are presented in Table 1. (FAR is reported as the mean value ± SEM of the individual calculated FARs) Figure 1 shows the comparative results. Fatal/anesthetic ratio was significantly lower (worse) for halothane (1.68) than for to isoflurane (3.12) in all groups, whether or not there was major surgery, critical coronary stenosis, or intermittent myocardial ischemia. Summarizing Figure 1, halothane's safety margin was approximately half that of isoflurane. Table 2 shows the number of animals surviving at least 10 min [Et] at each MAC increment. Table 3 gives *P* values for comparisons between the groups.

Comparing the closed chest animals (groups H_1 and I_1 to all open chest groups, the FAR for isoflurane was not significantly worse in the open chest groups. In contrast, when halothane was the anesthetic, there was a significant decrease of approximately 20% in FAR, from 1.98 ± 0.6 to 1.58 ± 0.07 for closed vs open chest animals, respectively. For each agent, there were no significant differences in FAR between any of the separate open chest groups. Again, a significantly lower FAR was found for halothane vs isoflurane in these open chest groups. Although the aortic snare elevated coronary driving pressure intermittently to levels equal to group averages at equi-MAC level in the previously studied isoflurane groups, the maneuver was not effective in increasing halothane's FAR when compared with either the isoflurane groups or with the other open chest halothane groups.

Addition of major surgical stress during different experiments involving open chest animals significantly lowered halothane's already significantly worse FAR relative to that of isoflurane. With isoflurane, addition of an apparently identical magnitude of surgical stress did not significantly decrease the isoflurane FAR seen in the control group (I_1). Blood gas tensions, pH, and temperatures were not significantly different between groups and/or across the time of the studies.

Discussion

A wider safety margin of isoflurane relative to halothane has been previously reported in rats (3,4) (without surgery or concomitant disease). Kissin et al. (4) found isoflurane's safety margin to be more than double that of halothane. Wolfson et al. (3) reported a safety margin for isoflurane of approximately 1.9 times that of halothane. Our overall fatal/anesthetic ratio for isoflurane was 1.88 times that of halothane in these large mammals.

Our calculation of safety margin depends on MAC. We used previously reported MAC values of 1.25% for halothane (9) and 1.45% for isoflurane (8). Tranquilli et al. (14), in contrast, reported a halothane MAC in pigs of 0.91%. This value was reported in much larger pigs (46–96 kg) than either we (32.6 ± 0.7 (SEM), range 24–39 kg) or Weiskopf and Bogets (9) (24.7 ± 1 kg) used. Porcine weight correlates with age. The lower MAC values of Tranquilli may reflect an older study group, as aging has been shown to lower MAC (15). Further, Tranquilli et al. (14) did not allow steady state equilibration for 15 min at each tested concentration; they instead assumed that a small alveolar to inspired difference indicated steady state. We believe the MAC of 1.25% determined by Weiskopf and Bogets (9) to be more relevant to our experiments and so chose to use it. Substitution of the Tranquilli et al. (14) halothane MAC of 0.91% in our FARs would move them closer to those seen with isoflurane but there still would be a substantial difference between agents, and surgery would have had the same relative further deleterious consequences with halothane but not with isoflurane.

Critical coronary stenosis was defined by Gould et al. (10) as a stenosis tight enough so that no reactive hyperemia occurs in response to a 10 sec total occlusion. This implies near maximal distal coronary dilation (in the absence of compensatory collateral flow) and greatly increased pressure dependency of coronary blood flow to the affected region. If ischemia had ensued because isoflurane indiscriminantly dilated other myocardial regions, as speculated to occur in human studies by Reiz et al. (16) and Moffit et al. (17), the isoflurane animals with critical coronary stenoses would have been expected to have a worsened fatal/anesthetic ratio. Because this did not occur, the production of significant myocardial ischemia with clinically relevant [Et] levels of isoflurane by a mechanism of coronary steal could not be shown in this series of experiments. One problem may be inadequacy of such a "critical" coronary stenosis. Hickey et al. (7) produced hypotension with nitroprusside, halothane, or trimethaphan in a canine model with a critical coronary stenosis as defined earlier. They could not produce ischemia with a critical coronary stenosis, but a more severe stenosis in combination with hypotension did result in regional lactate production and ST segment depression (7). It is possible that a more severe coronary stenosis might have had a greater effect on FAR of one or both agents.

Our study indicates that a single, acute, critical coronary stenosis does not seem to reduce volatile anesthetic safety margin. Because the presence of a single, acute, coronary stenosis does not mimic diffuse coronary artery disease, Reiz's reported deleterious effect of isoflurane (16) might require more widespread coronary arterial disease and/or collateralization (which itself may not have the same vascular response to volatile anesthetics as do normal coronary arteries). Human studies reporting deleterious effects of isoflurane may have confounded their results through a combination of large, uncontrolled decreases in coronary perfusion pressure, with resultant autoregulatory changes in coronary vascular tone, coupled with increased heart rates plus extensive coronary disease. Our attempt to control for the decrease in coronary perfusion pressure seen with halothane in group H_4 by temporarily increasing blood pressure mechanically via an aortic snare did not result in an improved fatal/anesthetic ratio for halothane.

Anesthesia without vs with surgery might logically be expected to produce different results with respect to anesthetic safety margin determinations. Catecholamine release, other stress hormonal activity, fluid shifts, and oxygenation are likely to be different between surgery vs no surgery with respect to the anesthetized state. Exogenous vasopressors including epinephrine and norepinephrine, with the exception of ephedrine and possibly of mephentermine, do not alter MAC (18). Whether surgical stress alters MAC or not is not testable, since the determination of MAC in animals requires an intermittently-applied maximal stimulus. Sternotomy is not such an intermittent stimulus, and it would be difficult to assess its effect on individual MAC determinations. We elected to use previously published MAC values without making adjustment for superimposed surgical stress.

With halothane, major surgery with protocols that included either intermittent periods of regional brief myocardial ischemia or a continuous critical coronary stenosis both resulted in significant worsening of the FAR. A worsening of isoflurane's safety margin was not seen in the same two open chest groups anesthetized with that agent. There is evidence that halothane may have specific deleterious effects that result in a decreased fatal/anesthetic index. Michenfelder

(19) investigated halothane's effect on cerebral blood flow and $CMRO_2$ in dogs and reported that high concentrations of halothane decreased $CMRO_2$ to near zero levels. They considered this a toxic effect (19). They could not achieve this with barbiturates (20) or isoflurane (21), but instead noted a leveling off of $CMRO_2$ despite increasing doses of anesthetic to similarly high levels. Thus there appear to be distinct qualitative differences between halothane and isoflurane, a contention supported by our results. Similarly, though halothane may deleteriously affect hepatic arterial blood flow and oxygenation, and Van Dyke (22) has suggested that this might play a role in the mechanism of halothane-associated hepatotoxicity, Gelman et al. (23) found that isoflurane causes either hepatic arterial dilation and/or better preserved hepatic autoregulatory ability than does halothane. Studies of coronary vascular reactivity from our laboratory (24) have consistently shown much better preservation of coronary reserve at graded increments of anesthetic with isoflurane than with equi-MAC concentrations of halothane. Thus we believe there is considerable support, but no consensus regarding the mechanism, for a qualitative as well as quantitative difference in safety margin between halothane and isoflurane.

The most striking finding of our study is the low fatal/anesthetic ratio, or safety margin, found for halothane. The calculated overall ratio of 1.9 between the FAR of the two drugs (3.15/1.68 for isoflurane/halothane, respectively) implies that isoflurane has a safety margin about 200% higher than does halothane. This finding, although from a different species, is in agreement with previous investigations (3,4) reporting the relation between the safety margins of these two drugs to be 1.9 or higher.

Previous studies of anesthetic safety margins (1–4), however performed, have been in the absence of both systemic or cardiac disease and surgery. The resultant safety margins would be considered low by clinicians familiar with other commonly used drugs. Digitalis, generally considered a very unsatisfactory drug from this point of view, has a human toxic therapeutic ratio similar to that reported for halothane in rats by Wolfson et al. (3) and Kissin et al. (4). Utilizing the median cited therapeutic level, the toxic therapeutic ratio for digoxin is 2.0 (25).

We believe that studies of relative safety margins may be useful in making clinical choices in patients with concurrent disease. In a recent review of human anesthesia-related cardiac arrest by Keenan and Boyan (26), there were 15 cardiac arrests attributed at least in part to anesthetic overdoses. Nine of these (60%) involved a volatile anesthetic (six halothane, two enflurane, one cyclopropane); three of these nine patients died. Lunn and his colleagues in Cardiff made a large study of anesthesia risk, involving reports on 108,878 anesthetics (27). The overall mortality related to anesthesia was 4.6 per 10,000 cases. Of 32 deaths judged to be totally due to anesthesia, 5 were considered "unavoidable." In the remaining 27 cases, although there were "avoidable" features, the investigators were often of the opinion that even if the avoidable features had not occurred, there would still have been a fatality (28). Keats (29) has pointed out that older admonishments such as Sir Robert MacIntosh's famous 1948 statement "I hold that there should be no deaths due to anesthesia" (30), imply that anesthetics should somehow be different from all other drugs and have no inherent risk of toxicity (i.e, an infinite safety margin). Keats (29) and Lunn et al. (27) seem to be implying that low anesthetic safety margins may be at least in part causative. Why use any drugs with such low safety margins? Pharmacologic determinations of safety margin do not tell the whole story. If the kinetics of a drug are such that postoperative ventilatory support is not needed, for example, the overall usage of that drug might be safer despite a low pharmacologic safety margin. Volatile agents will likely remain popular for these kinds of reasons—but comparative pharmacologic safety margin studies should still help regarding choice.

In conclusion, we found isoflurane to have a higher fatal/anesthetic ratio than halothane in each study group. Addition of critical coronary stenosis had no effect on the fatal/anesthetic ratio with either anesthetic. Elevating the coronary perfusion pressure in the halothane group to levels equal to those seen in the isoflurane group did not improve halothane's safety margin. Addition of surgical stress further narrowed the safety margin of halothane but not that of isoflurane. We have shown that there are qualitative and quantitative differences in safety margins between the two anesthetics, and that addition of surgical stress is also a determinant of safety margin. A doubling of pharmacologic safety margin, though still low compared, for example, to narcotics or benzodiazepines, does seem clinically important. The fact that similar increases in safety margin were observed in rats as well as in the large mammals we studied increases the likelihood that there is clinical relevance to these animal findings.

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Reversal by Atropine of Tetanic Fade Induced in Cats by Antinicotinic and Anticholinesterase Agents

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ALVES-DO-PRADO W, CORRADO AP, PRADO WA. Reversal by atropine of tetanic fade induced in cats by antinicotinic and anticholinesterase agents. Anesth Analg 1987;66:492–6.

The tetanic fade induced by intraarterial administration of neostigmine or by subparalyzing doses of d-tubocurarine or hexamethonium was studied in cat anterior tibial muscle preparations. The prior administration of atropine significantly reduced the time for recovery from the tetanic fade induced by the above mentioned drugs. A similar response was seen when atropine was administered prior to neostigmine administration for reversal of paralyzing doses of d-tubocurarine. We interpret these results to show that presynaptic muscarinic receptors participate in a negative feedback affecting acetylcholine release at the neuromuscular junction.

Key Words: NEUROMUSCULAR JUNCTION—function. NEUROMUSCULAR RELAXANTS—*d*-tubocurarine. PARASYMPATHOMIMETIC NERVOUS SYSTEM—atropine.

Skeletal muscles respond with sustained contractions when electrically stimulated at physiologic frequencies (30–80 Hz). However, tetanic fade (Wedensky inhibition) may follow nerve stimulation even at lower frequencies if muscle is treated with anticholinesterase (1) or antinicotinic agents (2).

Tetanic fade has been related to a run-down of endplate potentials and probably depends on a partial exhaustion of the readily releasable store of acetylcholine (Ach) (3,4). Theoretical models have been proposed suggesting that Ach, in addition to its action on subsynaptic membranes, also acts on prejunctional cholinoceptors to change the Ach mobilization process and thus to control the neurotransmitter output during tetanic stimulation. Nicotinic (5) and muscarinic presynaptic receptors (6,7) exist in motor nerve endings. The blockade of nicotinic presynaptic receptors by curarelike drugs decreases (8), whereas blockade of muscarinic presynaptic receptors by atropine increases, Ach output from neuromuscular preparations (9).

Atropine is usually clinically employed together with an anticholinesterase for reversal of nondepolarizing muscle relaxants. However, there are no reports documenting interactions between atropine, muscle relaxants, and cholinesterase antagonists at the neuromuscular synapse. The present study was undertaken to analyze further in the cat anterior tibial muscle preparation the effect of atropine on the recovery of tetanic fade induced by *d*-tubocurarine, hexamethonium, or neostigmine.

Methods

Cats of either sex, weighing 3–4.5 kg, were used in this study. Each animal was anesthetized with a combination of α-chloralose 60 mg/kg IV, and urethane, 600 mg/kg IV. The anterior tibial muscle was then prepared for the recording of isometric twitch tension by means of a previously described method (10). The right limb was fixed to a Brown–Schuster-type myograph by means of a metal pin screwed through the head of the tibia. The distal tendon was dissected free and tied to a force-displacement transducer coupled to a Grass 5D polygraph (Grass Instruments, Quincy, MA). The popliteal artery was exposed and all branches except those to the anterior tibial muscle and the middle genicular artery were tied off. To allow intraarterial injection of drugs, a polyethylene cannula was introduced into the middle genicular artery and tied close to the popliteal artery. During intraarterial in-

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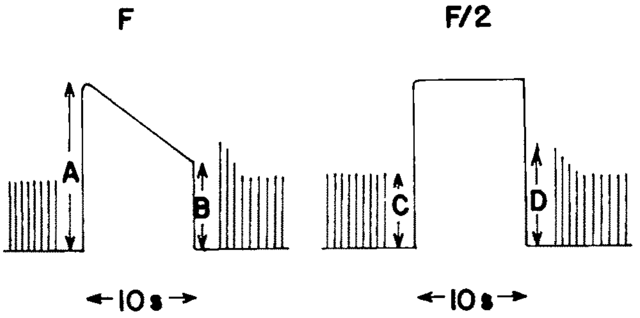

Figure 1. Examples of cat anterior tibial muscle contractile response during tetanic stimulation. The tetanic fade is calculated as the ratio (R) between the tension at the end (B) and the tension at the beginning (A) of the tetanic response (R = B/A). C and D correspond to pretetanic and posttetanic twitches, respectively. F represents the rate of stimulation required to obtain R = 0.5.

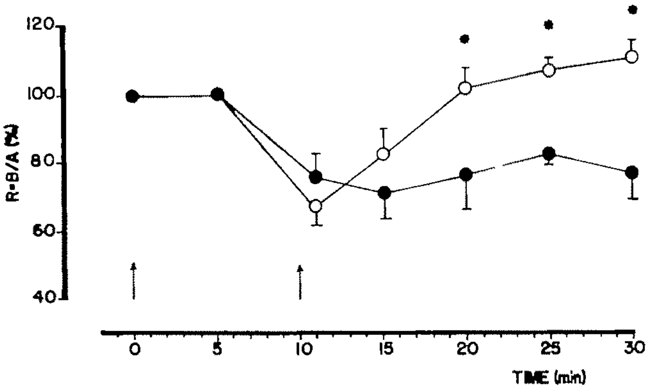

Figure 2. Antagonism by atropine, 0.25 μg/kg, of tetanic fade induced by neostigmine, 1.0 μg/kg, in cat anterior tibial muscle preparations. In the ordinate, ratio R (see Fig. 1) is expressed as a percentage of that obtained 5 min after injection of drug-free saline, taken as 100%. The abcissa represents time after injection of drug-free saline (●—●) or saline containing atropine (○—○). Neostigmine was injected at time t = 10 min (arrow). Drugs were administered through the middle genicular artery. Points represent mean (± SE) of 6 experiments. *Significantly different from control (drug-free saline) for $P < 0.05$.

jection of drugs, the anterior tibial artery was occluded just below the entrance of its branch into the anterior tibial muscle.

Muscular contractions were evoked by electrical stimulation of the sciatic nerve with supramaximal square wave pulses of 0.05 msec duration. In all experiments the standard rate of stimulation was 0.1 Hz, but at 5 min intervals there was stimulation at higher (tetanic) rates applied to the nerve for 10 sec. The tension produced at the beginning of tetanic stimulation (component A) was compared to that obtained at the end of tetanic stimulation (component B). The rate of stimulation (F) required to obtain a ratio R = B/A = 0.5 was determined for each preparation (see typical example in Fig. 1). The rate F/2 was then used throughout the experiment. Because values of R exceeding 1 were never detected, component A of the response to tetanic stimulation is also referred to in the text as tetanic peak tension. Saline (0.05 ml) was then injected intraarterially (time t = 0 min). Tetanic stimulation at F/2 Hz frequency was then applied to the nerve for 10 sec at t = 5 min. Test drug (neostigmine, hexamethonium, *d*-tubocurarine, or α-bungarotoxin) was injected intraarterially at t = 10 min. Doses of test drugs were chosen to change the ratio R without pronounced changes in twitch response. Tetanic stimulation was then repeated at t = 11, 15, 20, 25 and 30 min. During the intervals between consecutive tetanic stimulations, preparations were continuously stimulated at the standard rate. The same sequence was repeated 60 min later with saline-containing atropine injected at t = 0 min. Variations in R were expressed as a percentage of R obtained at t = 5 min in the absence of atropine and plotted against the time after test drug administration.

A different experimental design was used in a separate group of cats. The F/2 rate of stimulation was initially determined for each preparation. The cats were then divided into three groups (groups 1 through 3), each one beginning at time t = 0 with the administration of a paralyzing dose of *d*-tubocurarine intraarterially followed by tetanic stimulation delivered at t = 1, 5, 10, 15, 20, 25 and 30 min. A standard rate of stimulation was used during the intervals. Drug-free saline was injected by the same route at t = 4 and at t = 9 min in group 1 (control) and at t = 4 min in group 2. Saline-containing neostigmine was injected at t = 9 min in groups 2 and 3. Saline-containing atropine was injected at t = 4 min in group 3. The sequence of experiments was arranged in a random manner for each preparation. No stimulation was applied to the motor nerve during the 30-min rest period between experiments. Variations in R were expressed as a percentage of that R obtained 5 min before administration of *d*-tubocurarine and plotted as described above. All test drugs were dissolved in saline (0.05 ml) and injected as a bolus followed by washing of the cannula with drug-free saline (0.05 ml).

Rectal temperature were maintained at 37 ± 1°C throughout the experiment. All exposed tissues in the preparation were covered with mineral oil. The data obtained in the absence (control) or presence of test drug (neostigmine, hexamethonium, or *d*-tubocurarine) were subjected to analysis of variance. The data obtained from different groups of cats were submitted to an ANOVA II analysis of variance for repeated measures in randomized block designs. Tuckey's test

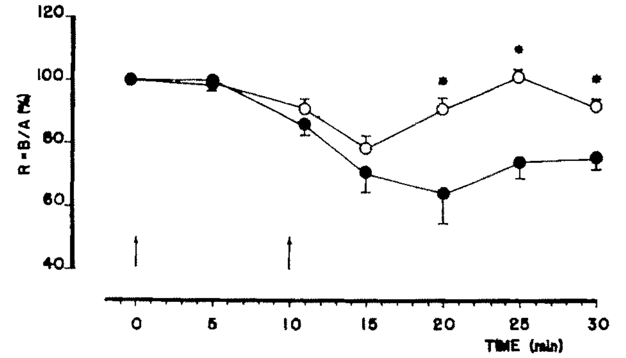

Figure 3. Antagonism by atropine, 0.3 μg/kg, of tetanic fade induced by hexamethonium, 10 μg/kg, in cat anterior tibial muscle preparations. Ordinates and abcissae are as in Figure 2. Hexamethonium was injected at time t = 10 min (arrow). Drugs were injected through the middle genicular artery. Points are means (±SE) of six experiments. *Significantly different from control (drug-free saline) ($P < 0.05$).

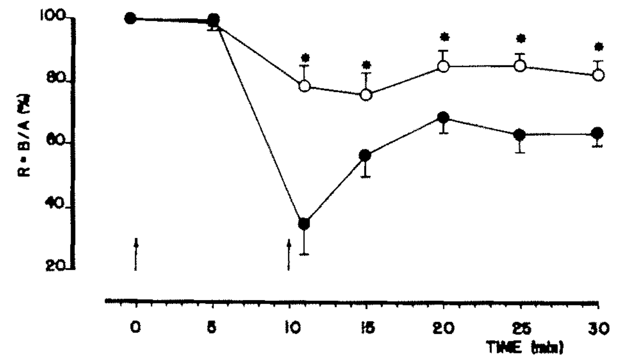

Figure 4. Antagonism by atropine, 1.0 μg/kg, of tetanic fade induced by *d*-tubocurarine, 4.0 μg/kg, in cat anterior tibial muscle preparations. Ordinates and abcissae are as in Figure 2. *d*-Tubocurarine was injected at time t = 10 min (arrow). Drugs were administered through the middle genicular artery. Points are means (±SE) of six experiments. *Significantly different from control (drug-free saline) ($P < 0.05$).

was applied when control and test data were significantly different by analysis of variance.

The following drugs were used: atropine sulphate (Merck), *d*-tubocurarine chloride, hexamethonium bromide, neostigmine methyl-sulphate and α-bungarotoxin (Sigma). All doses were given as the salt.

Results

Effect of Neostigmine

The tetanic tension of cat anterior tibial muscle during nerve stimulation at rate F/2 (40–80 Hz) was usually well sustained. After neostigmine, 10 μg/kg intraarterially, a tetanic fade was observed. The tetanic peak tension was not changed by the anticholinesterase agent, and twitches evoked by the standard rate of stimulation were increased slightly and only transiently. The decrease in R values was maximal 5 min after drug administration and remained below the control levels for 20 min. Spontaneous recovery was complete 60 min after neostigmine (not shown in figures). Maximal decrease in R occurred sooner when atropine, 0.25 μg/kg intraarterially, preceded the injection of neostigmine. Complete recovery followed by R values slightly above control levels occurred 10 min after neostigmine in atropine-treated preparations (Fig. 2). Atropine alone had no effect on either twitch or tetanic tension.

Effect of Hexamethonium

Hexamethonium, 10 μg/kg, intraarterially, induced tetanic fade with no detectable change in either tetanic peak tension or the twitches evoked by a standard rate of stimulation. Maximal reduction in R was obtained 10 min after drug administration and remained below control for about 50 min. Similar degrees of fade were seen when hexamethonium was administered after atropine, 0.3 μg/kg intraarterially. The maximum decrease in R at 1 and 5 min after hexamethonium and atropine was only slightly less than in controls. However, complete recovery ocurred significantly earlier in the presence of atropine (Fig. 3).

Effect of d-Tubocurarine

d-Tubocurarine, 4.0 μg/kg intraarterially, produced tetanic fade after a slight and transitory depression of twitch but not in tetanic peak tension. Maximal decrease in R was observed 60 sec after drug administration and spontaneous recovery was complete 60 min later. Tetanic fade induced by *d*-tubocurarine was significantly less and appeared earlier when the drug was administered after atropine, 1.0 μg/kg intraarterially. Although recovery was not completed during the time of observation, the R values were always significantly greater than in controls (Fig. 4).

Effect of α-Bungarotoxin

α-Bungarotoxin, 10 μg/kg intraarterially, produced slow and progressive depression of both twitch and tetanic peak tensions but not of tetanic fade (not shown in figures). These effects were not changed by the previous administration of atropine, 1.0–6.0 μg/kg intraarterially, in the six animals tested.

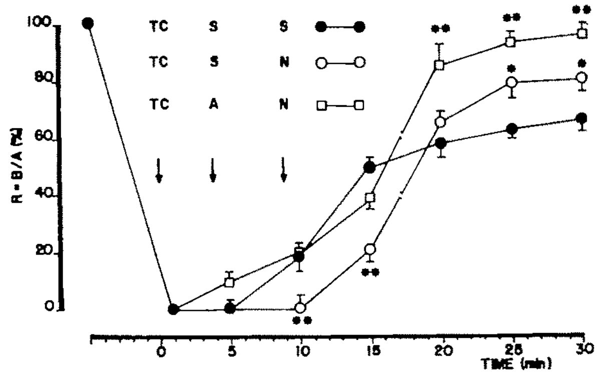

Figure 5. Tetanic fade induced by paralyzing dose of *d*-tubocurarine (TC = 80 μg/kg). On the ordinate axis, ratio R (see Fig. 1) is expressed as percentage of R obtained before TC administration (control) in each experimental sequence, taken as 100%. The abcissa expresses time after injection of TC. Arrows indicate time of injection of TC, drug-free saline (S = 0.05 ml), or saline containing neostigmine (N = 60 μg/kg) or atropine (A = 40 μg/kg) through the middle genicular artery. Points are means (±SE) of six experiments. Asterisk denotes significantly different from control curve (●—●), double asterisk denotes significantly different from any other curve at the same time of observation.

Antagonism by the Combination of Atropine and Neostigmine of Tetanic Fade Induced by d-Tubocurarine

d-Tubocurarine, 80 μg/kg intraarterially, was used to block twitches and produce a tetanic fade that spontaneously recovered within 60 min. Artificial respiration was not required under these experimental conditions. In group I, R values that were virtually zero were obtained 1 and 5 min after *d*-tubocurarine (Fig. 5). Neostigmine, 60 μg/kg, injected intraarterially 9 min after *d*-tubocurarine led to prompt recovery of twitch tension (not shown in figures) but transiently prolonged the time for recovery from tetanic fade. R values significantly greater than those seen in group I were obtained only 25 and 30 min after *d*-tubocurarine (Fig. 5). Atropine, 40 μg/kg intraarterially, not only shortened the time for recovery from the tetanic fade but also hindered the neostigmine-induced transitory potentiation of tetanic fade produced by *d*-tubocurarine (Fig. 5). Analysis of variance applied to the data indicates that the curves in Figure 5 are significantly different ($P < 0.01$).

Discussion

The present results demonstrate that atropine reduces the time for recovery from tetanic fade induced by *d*-tubocurarine, hexamethonium, or neostigmine in cat tibialis anticus muscle preparations. Confirming previous reports (2), the tetanic fade occurred even when doses of drugs used were insufficient to produce prominent changes in twitch tension. It was also shown that neostigmine, although leading to prompt recovery of the twitch tension, transiently potentiates the tetanic fade induced by a paralyzing dose of *d*-tubocurarine. Atropine not only hindered the potentiation produced by neostigmine but also hastened the recovery from tetanic fade initially produced by *d*-tubocurarine.

Over the years, several reports have presented evidence suggesting that tetanic fade may result from postjunctional or prejunctional effects of drugs. The former hypothesis, that the effect is postjunctional, includes the proposal that Ach released during high frequencies of nerve stimulation may promote an increased frequency of ion channel opening (11). Recent evidence indicates that *d*-tubocurarine not only interacts with the receptor sites of the closed form of the receptor but also penetrates and plugs open ion channels (12). Hexamethonium appears to act mainly by plugging the open ion channels (13,14). The plugging of the ion channels by these antagonists would be facilitated during tetanic nerve stimulation, thus producing fade. Confirming a previous report (15), we have also demonstrated that α-bungarotoxin depressed both twitch and tetanic tension but did not produce fade. This toxin is thought to combine with receptor recognition sites but probably does not penetrate the open ion channels (16). Fade would then depend on increased plugging of open ion channels by the antagonist, but not on blockade of receptor recognition sites (2). If this is so, the fade induced by neostigmine might result from an increased channel opening by Ach accumulated in the synaptic cleft. A desensitization of subsynaptic membranes should then be expected (1), but this phenomenon was not shown to follow high frequencies of nerve stimulation (17,18). Moreover, we would expect atropine to enhance the fade induced by neostigmine, *d*-tubocurarine, or hexamethonium, because atropine is known to block open ion channels in the motor endplate (11). Thus, a postjunctional mechanism of interaction does not seem likely to account for the results we found in our study.

The ability of atropine to enhance the Ach release from the cerebral cortex (19–21) has led to the concept of a muscarinic feedback inhibition over Ach release (22), an hypothesis also extended to smooth (23) and skeletal muscles (9). There is also evidence that a nicotinic feedback excitation over Ach release may also exist at the neuromuscular junction (see introduction). Taken together, these reports led us to conclude that during physiologic rates of nerve stimulation neuromuscular transmission depends on a presynaptic modulation of Ach release involving both nicotinic and muscarinic feedback mechanisms. The former feedback is related to an increase in the neurotransmitter output from its readily releasable storage sites (2), whereas the latter, in accordance with experiments on Torpedo synaptosomes, may be related to the inhibition of metabolic reactions that regulate Ach mobilization (7). The Ach accumulated in the synaptic cleft may then stimulate or inhibit its own release, especially in the presence of high frequencies of nerve stimulation. According to this point of view, blockade by *d*-tubocurarine or hexamethonium of presynaptic nicotinic receptors leaves unaffected the muscarinic receptors through which Ach reduces its output and produces fade. The neostigmine-induced fade would then be explained as a reinforcement of the natural tendency of high frequencies of nerve stimulation to stimulate presynaptic muscarinic receptors.

In summary, our data indicate that atropine may well play a role in clinical anesthesia when given together with an anticholinesterase to reverse the action of a nondepolarizing relaxant.

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Postoperative Confusion after Anesthesia in Elderly Patients with Femoral Neck Fractures

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BERGGREN D, GUSTAFSON Y, ERIKSSON B, BUCHT G, HANSSON L-I, REIZ S, WINBLAD B. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg 1987;66:497–504.

Fifty-seven patients, all over the age of 64, with femoral neck fracture were randomized to receive epidural or halothane anesthesia to see if the anesthetic technique influenced the incidence of postoperative confusion. All patients were lucid on admission. Using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III) as criteria for confusion, we found that 44% of the patients developed confusion that correlated closely to a history of mental depression ($P < 0.01$) and to the use of drugs with anticholinergic effect ($P < 0.005$). There was no difference in the incidence of confusion between the two anesthetic groups. In patients given halothane, however, early postoperative hypoxemia was associated with confusion ($P < 0.05$). Patients with confusion had significantly more postoperative complications and almost four times longer hospitalization times. It is concluded that anticholinergic medication and a history of mental depression are predominant risk factors for development of postoperative confusion and in this respect are more important than the anesthetic technique.

Key Words: RECOVERY—delirium, confusion. PSYCHOLOGIC RESPONSES—delirium, confusion. ANESTHESIA, ORTHOPEDIC—hip fractures. ANESTHESIA—geriatric.

Postoperative confusion in elderly patients after surgery for fractured neck of the femur is a well-known clinical problem. The incidence of femoral neck fractures is increasing because of the expanding elderly population. During the past two decades, there also has been a non-age-related increase in the incidence of hip fractures in urban populations of the Scandinavian countries and Great Britain (1–5). Postoperative cardiopulmonary complications and mortality have been extensively studied in such patients (6–10). In contrast, there is little information available on the mechanisms of postoperative mental complications in these patients. In elderly patients operated on for hip fractures, under a variety of anesthetic agents and techniques as well as with different surgical methods, 36% (33/91) were confused on the first postoperative day (11). Cognitive impairment seems to be the most reliable predictor for patients not regaining independence after hip fracture surgery (12–14).

It has been suggested that the anesthetic technique may be of importance in the development of postoperative mental confusion. A significantly higher incidence of mental complications after elective hip replacement surgery was found in patients anesthetized with thiopental–fentanyl–nitrous oxide than in patients operated on under epidural analgesia (15). The authors concluded that confusion was related to the degree of postoperative hypoxemia in patients given general anesthesia. Anticholinergic medication has also been associated with postoperative confusion (16).

The aim of the present study was to compare the incidence of postoperative mental confusion and associated complications in patients operated on for fractured neck of the femur under halothane and under epidural anesthesia.

Materials and Methods

Fifty-seven patients admitted to the orthopedic wards of the Umeå University Hospital from March 1983 to November 1984 were followed from admission until 1 yr after surgery. All patients were operated on for femoral neck fractures. Only fully lucid patients were

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Table 1. Patient Data

	Epidural group (n = 28)		Halothane group (n = 29)	
Age (yr)	78 ± 8		77 ± 7	
Range	65–92		66–86	
Sex F/M	24/4		22/7	
Previous medical history	Confusion (n = 14)	No confusion (n = 14)	Confusion (n = 11)	No confusion (n = 18)
Ischemic heart disease	10	8	5	6
Hypertension	4	2	2	5
Diabetes	1	3	2	3
Cerebrovascular disease	3	1	—	2
Respiratory disease	2	1	—	2
Depression	6	1	2	1
Parkinsonism	1	1	3	—
Severely impaired hearing	1	2	3	5
Severe visual impairment	4	2	1	3
Medication	Confusion (n = 14)	No confusion (n = 14)	Confusion (n = 11)	No confusion (n = 18)
Digitalis	4	2	2	5
β-blockers	3	1	1	3
Diuretics	4	5	5	6
Insulin or oral antidiabetic drugs	—	2	2	1
Antiparkinson drugs	—	2	3	—
Benzodiazepines	4	1	3	3
Drugs with anticholinergic action[a]				
Antidepressants	6	—	2	—
Neuroleptics	6	2	2	1
Others	1	1	1	—
No medication	—	3	1	5

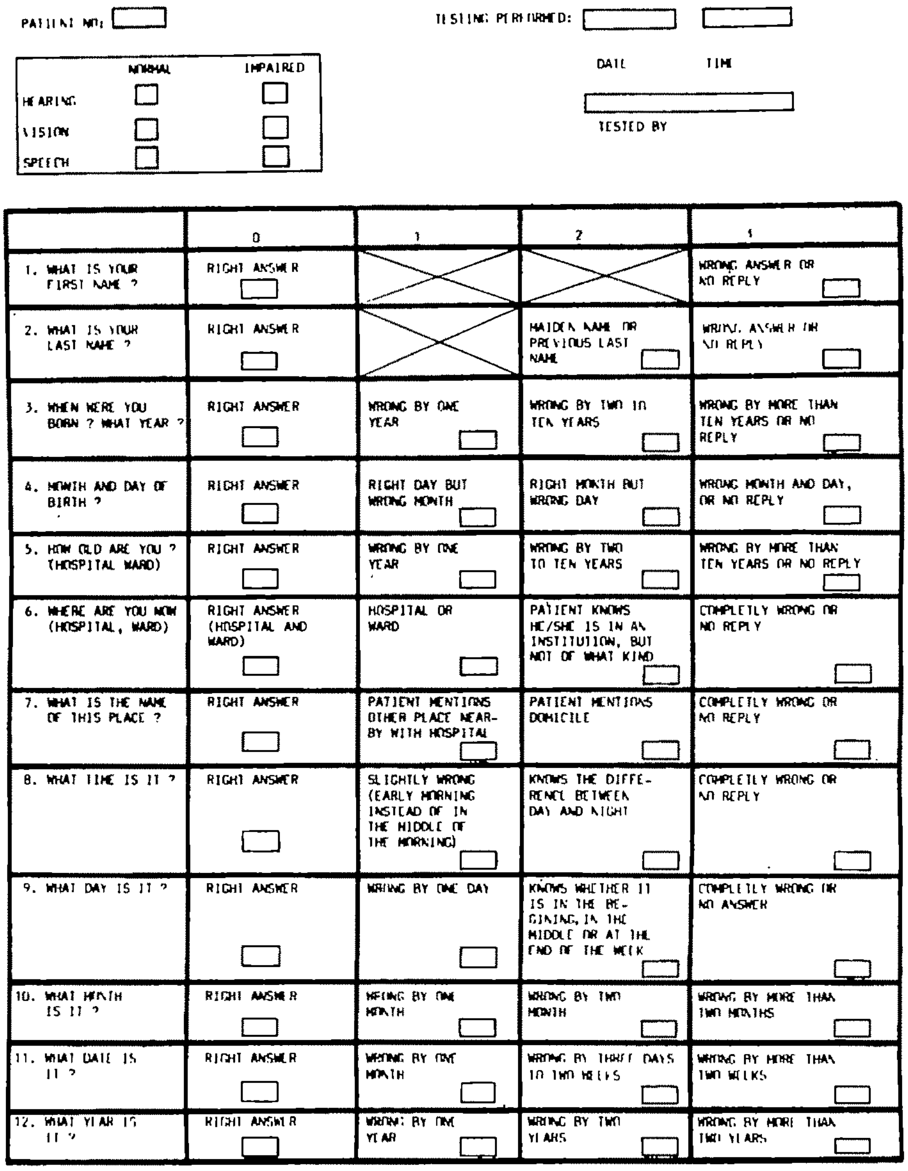
[a] Drugs with anticholinergic action were significantly more common in the epidural group ($P < 0.05$).

included in the study. After informed consent, patients were randomly allocated to receive either halothane or epidural anesthesia. Relevant patient data are outlined in Table 1. The study was approved by the Ethics Committee of the University of Umeå.

Mental Testing

In accordance with the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) criteria for delirium (17), patients were defined as confused if they had clouding of consciousness and were disoriented as to their own identity, to time, or to situation, and if the mental symptoms fluctuated. The Organic Brain Syndrome Scale (OBS scale) developed by Gustafson (18) was used to detect and follow confusion. The OBS scale consists of two parts: the disorientation subscale, a questionnaire of 15 items; and the confusion subscale, an observation schedule containing 39 clinical features. The disorientation subscale describes the patient's orientation as to time, place, and own identity and the confusion subscale describes different cognitive, perceptual, emotional, and personality changes, physical and practical disabilities, and fluctuations of the clinical state. The items are rated on a four-point scale. A nondisturbed behavior or correct answer results in a zero (0): most disturbed behavior or a totally incorrect answer is assigned three points, as is no answer given.

In the present study, variables of the OBS scale affected by the hip fracture per se were excluded. Thus, the disorientation subscale (Fig. 1) was modified to 12 and the confusion subscale to 21 items. Patients were tested on admission with the 12-item disorientation subscale. Only those with six points or less (36 points = total disorientation), in a maximum of three variables, were included in the study. The mean score was 1.5 points. The first testing was done within 3 hr of admission. All 33 variables were recorded on the first and seventh postoperative days. Recovery from drugs used in anesthesia usually is complete after 8 hr (19,20), and so any abnormal mental states seen within the first eight postoperative hours were not registered as confusion. Patients were tested



PATIENT NO: ☐

TESTING PERFORMED: ☐ DATE ☐ TIME

☐ TESTED BY

	NORMAL	IMPAIRED
HEARING	☐	☐
VISION	☐	☐
SPEECH	☐	☐

	0	1	2	3
1. WHAT IS YOUR FIRST NAME ?	RIGHT ANSWER ☐			WRONG ANSWER OR NO REPLY ☐
2. WHAT IS YOUR LAST NAME ?	RIGHT ANSWER ☐		MAIDEN NAME OR PREVIOUS LAST NAME ☐	WRONG ANSWER OR NO REPLY ☐
3. WHEN WERE YOU BORN ? WHAT YEAR ?	RIGHT ANSWER ☐	WRONG BY ONE YEAR ☐	WRONG BY TWO TO TEN YEARS ☐	WRONG BY MORE THAN TEN YEARS OR NO REPLY ☐
4. MONTH AND DAY OF BIRTH ?	RIGHT ANSWER ☐	RIGHT DAY BUT WRONG MONTH ☐	RIGHT MONTH BUT WRONG DAY ☐	WRONG MONTH AND DAY, OR NO REPLY ☐
5. HOW OLD ARE YOU ? (HOSPITAL WARD)	RIGHT ANSWER ☐	WRONG BY ONE YEAR ☐	WRONG BY TWO TO TEN YEARS ☐	WRONG BY MORE THAN TEN YEARS OR NO REPLY ☐
6. WHERE ARE YOU NOW (HOSPITAL, WARD)	RIGHT ANSWER (HOSPITAL AND WARD) ☐	HOSPITAL OR WARD ☐	PATIENT KNOWS HE/SHE IS IN AN INSTITUTION, BUT NOT OF WHAT KIND ☐	COMPLETLY WRONG OR NO REPLY ☐
7. WHAT IS THE NAME OF THIS PLACE ?	RIGHT ANSWER ☐	PATIENT MENTIONS OTHER PLACE NEARBY WITH HOSPITAL ☐	PATIENT MENTIONS DOMICILE ☐	COMPLETLY WRONG OR NO REPLY ☐
8. WHAT TIME IS IT ?	RIGHT ANSWER ☐	SLIGHTLY WRONG (EARLY MORNING INSTEAD OF IN THE MIDDLE OF THE MORNING) ☐	KNOWS THE DIFFERENCE BETWEEN DAY AND NIGHT ☐	COMPLETLY WRONG OR NO REPLY ☐
9. WHAT DAY IS IT ?	RIGHT ANSWER ☐	WRONG BY ONE DAY ☐	KNOWS WHETHER IT IS IN THE BEGINING, IN THE MIDDLE OR AT THE END OF THE WEEK ☐	COMPLETLY WRONG OR NO ANSWER ☐
10. WHAT MONTH IS IT ?	RIGHT ANSWER ☐	WRONG BY ONE MONTH ☐	WRONG BY TWO MONTH ☐	WRONG BY MORE THAN TWO MONTHS ☐
11. WHAT DATE IS IT ?	RIGHT ANSWER ☐	WRONG BY ONE MONTH ☐	WRONG BY THREE DAYS TO TWO WEEKS ☐	WRONG BY MORE THAN TWO WEEKS ☐
12. WHAT YEAR IS IT ?	RIGHT ANSWER ☐	WRONG BY ONE YEAR ☐	WRONG BY TWO YEARS ☐	WRONG BY MORE THAN TWO YEARS ☐

Figure 1. The disorientation subscale of the rating scale for organic brain syndromes (L. Gustavsson) modified to patients with femoral neck fractures. On admission 26 patients answered all these questions fully correctly, rendering a score of zero points. Only one patient had six points.

according to the modified OBS scale by two of the authors (Gustafson, Bucht). Their interrater reliability was tested before and during the study and was found to be over 90% for all variables. At the time of testing, they did not know what type of anesthesia the patients had been given. All patients were interviewed 6 and 12 months after surgery with regard to their living conditions and walking ability.

Preoperative Evaluation and Anesthetic Techniques

Preoperative chest x-ray, 12-lead ECG, and blood chemistries (hemoglobin, hematocrit, electrolytes, and arterial blood gas tensions while breathing room air) were obtained in all patients.

Dextran 70 as antithrombotic therapy was started before surgery. Premedication was 25–50 mg meperidine approximately 30 min before induction of anesthesia. In the epidural group, standard loss of resistence technique was used to identify the epidural space of L3–L4 or L4–L5 and a catheter inserted. After a 5-ml test dose of prilocaine (20 mg/ml) with epinephrine (5 μg/ml), a bolus dose of the same agent was administered based on age and weight (total mean volume 12.5 ml, range 9–21 ml). If necessary, an additional dose of either prilocaine or bupivacaine (5 mg/ml) with epinephrine, at half the initial volume, was given through the epidural catheter 75 min later. The epidural catheter was removed as the patient left the operating room.

In the general anesthesia group, anesthesia was induced with thiopental 3–4 mg/kg IV after preoxgen-

Table 2. Postoperative Complications

	Epidural analgesia (n = 28)		Halothane anesthesia (n = 29)		Grand total (n = 57)	
	Number	Percentage	Number	Percentage	Number	Percentage
Confusion	14	50	11	38	25	44
Mental depression	3	11	3	10	6	11
Urinary incontinence	6	21	5	17	11	19
Urinary retention	5	18	6	21	11	19
Urinary catheter more than 12 hr postoperatively	21	75	14	48*	35	61
Urinary tract infection	9	32	7	24	16	28
Urosepsis	1	4	—	—	1	2
No urinary problems	3	11	9	31	12	21
Decubitus ulcer	3	11	5	17	8	14
Stroke	3	11	—	—	3	5
Feeding problems	1	4	1	3	2	4

*Significantly less common than in the epidural group ($P < 0.05$).

ation and 0.25–0.5 mg atropine IV. Tracheal intubation was performed after succinylcholine 1 mg/kg IV, after which respiration was mechanically controlled until the completion of surgery. Halothane was administered as required in nitrous oxide/oxygen (50/50) using a nonrebreathing system. Muscle relaxation was provided with a succinylcholine infusion (1 g in 500 ml 5% dextrose in water). End-tidal carbon dioxide tension was monitored and kept at normal levels. The V5 ECG was continuously monitored during anesthesia. Extubation was performed in the operating room and all patients were moved to the recovery room.

In both groups, a perioperative arterial specimen for measurement of gas tensions was drawn during steady-state anesthesia. Hypotension (more than 30% below preanesthetic noninvasive systolic control levels) was in the halothane group treated primarily with crystalloids and/or change in depth of anesthesia. In the epidural group with crystalloids, incremental IV doses of 5–10 mg ephedrine were given if necessary to treat hypotension.

Surgical Technique

If necessary, the fracture was reduced under biplane fluoroscopy. For fixation, either hookpins (21,22) or von Bahr screws (23) were used. In two patients with fractures close to the trochanteric area, fixation was achieved with a sliding screw and a plate.

Postoperative Care

Patients were kept in the recovery room for 4 hr and then sent to the orthopedic ward. Arterial samples were drawn with the patients breathing room air 30 min and 4 hr postoperatively and on the first, third, and seventh postoperative days. Clinical complications were recorded as shown in Table 2. The occurrence of postoperative pulmonary embolism, cardiac failure, and/or pneumonia was also noted. If possible, patients were mobilized on the first postoperative day.

Table 3. Mean Maximal Reduction in Systolic Blood Pressure Recorded During Anesthesia

	Percentage reduction from preanesthetic control
Epidural (n = 28)	37 ± 13
Halothane (n = 29)	30 ± 9*

*$P < 0.05$ compared with the epidural group.

Statistics

The χ^2-test, one-way analysis of variance, multiple regression analysis, and the Wilcoxon and Mann-Whitney tests were used for the statistical analyses of the results, which are presented as the means ± SD. A P value of less than 0.05 was regarded as statistically significant.

Results

The two groups were comparable with regard to age, sex, preexisting diseases, and preoperative medications (Table 1), except for drugs with anticholinergic effects, which were used significantly more frequently in the epidural group ($P < 0.05$). No differences between the groups were found in any of the preoperative laboratory tests or ECG and chest x-rays. Forty-two of the patients (74%) were operated on within 36 hr of sustaining their fractures. The majority of the

Table 4. Changes in Systolic Blood Pressure during Anesthesia

	Less than 30% reduction	Greater than 30% reduction for less than 15 min	Greater than 30% reduction for longer than 15 min but responding to treatment	Greater than 30% reduction throughout anesthesia, not responding to treatment
Epidural (n = 28)	10	5	9	4
Halothane (n = 29)	16	8	5	—

remaining patients were operated on within 72 hr. The mean operating time was similar in the two groups (general anesthesia 31 ± 10 min, epidural analgesia 35 ± 10 min). Intraoperative blood loss was minimal except for three patients who had 300–400 ml blood loss. The magnitude of perioperative hypotension was significantly greater in the epidural group (Table 3). The duration of hypotension was, however, not statistically different between the groups (Table 4).

Five patients (three epidural, two general anesthesia) developed mental confusion after initial testing but before anesthesia and surgery; the confusion persisted after surgery. These patients were obviously confused preoperatively, and their behavior as noted by doctors and nurses on the orthopedic and anesthetic wards was the same preoperatively as it was postoperatively when the mental testing was performed. Of the remainder, 13 patients became confused on the first postoperative day. Another seven patients developed confusion within the first week. There was no statistically significant difference in the incidence of confusion between the two anesthetic groups (11/29 in the halothane group and 14/28 in the epidural group) (Table 2).

Although there were no differences in the mean values of the preoperative blood gas tensions, 13 patients were hypoxemic when the first arterial blood sample was drawn; seven of them were later given general anesthesia and six given epidural anesthesia had arterial oxygen tensions below 8 kPa = 60 mm Hg. Perioperative arterial oxygen tension was significantly higher in the halothane group administered 50% oxygen. In the epidural group, intraoperative and postoperative blood gas tensions were not different from the preoperative values and no differences were observed between patients with or without confusion (Fig. 2). In the halothane group, patients who developed postoperative confusion had had significant decreases in arterial oxygen tension 30 min after anesthesia; the values then gradually returned to normal over the first postoperative week. Patients from both groups without postoperative confusion had no significant changes in arterial oxygen tensions during the study period. There was no difference in arterial oxygen tensions between patients with confusion in the two anesthetic groups. Fourteen of the patients given general anesthesia and ten of the epidural patients had arterial oxygen tensions below 8 kPa (60 mm Hg) at 30 min and/or 4 hr postoperatively.

Three of the epidural patients developed signs of stroke on the first postoperative day compared with none in the general anesthesia group. In one patient, who also had a previous history of cerebrovascular disease, this complication could be attributed to intraoperative hypotension. This patient had for 45 min a reduction in systolic blood pressure of more than 30% below baseline levels, 160 mm Hg.

Although the use of urinary bladder catheterization for more than the first 12 postoperative hours was significantly more frequent in the epidural group ($P < 0.05$), urinary tract infections were not more common in this group (Table 2).

Regression analysis did not reveal any correlation between mental confusion and age, preexisting nonmental diseases, hypotension, or anesthetic technique. In contrast, there was a close correlation between development of mental confusion and a history of mental depression ($P < 0.01$). On admission, regular and daily medication with antidepressants and/or neuroleptics correlated with development of mental confusion ($P < 0.0005$ and $P < 0.05$, respectively). When all regular medications with drugs with anticholinergic effects were considered, there was also a close correlation with postoperative confusion ($P < 0.005$). The drugs with anticholinergic effects were, in addition to antidepressants and neuroleptics, sleeping pills and perorally used anticholinergics for treatment of urinary incontinence. When patients treated with anticholinergic medications were excluded, there was still no correlation between anesthetic technique and confusion. In the general anesthesia group, confusion correlated with early postoperative hypoxemia ($P < 0.05$) (Fig. 2).

In the epidural group, during the postoperative period two patients were treated for pulmonary embolism, two were treated for cardiac failure, and one was treated for pneumonia. In the halothane group, two patients were treated for postoperative pneumonia.

There was no difference in duration of hospital stay

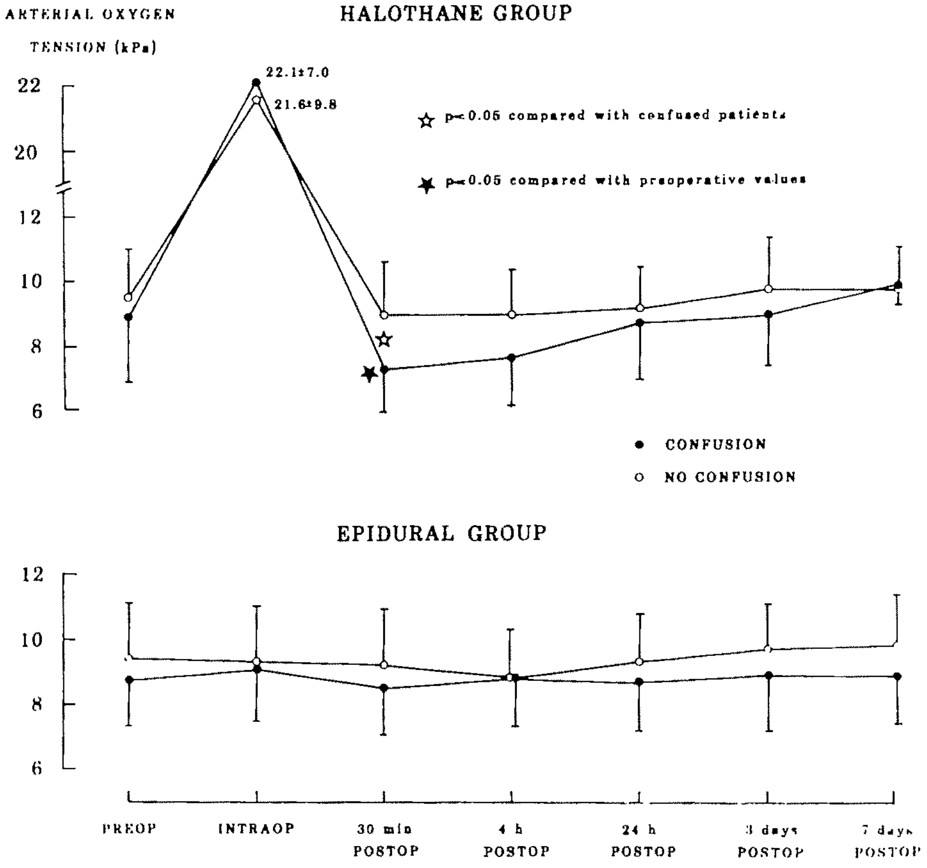


Figure 2. Pre-, peri-, and postoperative arterial oxygen tensions in patients operated on for femoral neck fracture under halothane anesthesia ($n = 29$) or epidural analgesia ($n = 28$). In patients anesthetized with halothane, postoperative confusion ($n = 11$) correlated with early postoperative hypoxemia ($P < 0.05$). Results are means ± SD.

between the two anesthetic groups. Patients who developed mental confusion had significantly longer periods of hospitalization on the orthopedic ward (mean value 24.5 vs 13.2 days, $P < 0.01$). Twelve percent of patients without mental confusion were transferred to a geriatric rehabilitation center as compared with 54% of patients with confusion. The mean total duration of hospital stay related to the fracture, during the 1-yr observation period for previously nonhospitalized patients, was 77 days (range 8–365) and 22 days (6–161) in the confused and nonconfused patients, respectively ($P < 0.0001$).

The total 1-yr mortality was 7% (4/57). One confused patient (92 yr of age) in the epidural group died of circulatory failure on the first postoperative day. The three remaining patients (all older than 84 yr), one of whom had postoperative confusion, died some 5 months postsurgery.

Discussion

The most striking finding in the present study was the high incidence of postoperative mental confusion with the associated prolonged duration of hospital stay in both groups. Despite the selection of patients without signs of mental confusion or dementia on admission and the use of short operative procedures, 35% (20/57) developed confusion during the first postoperative week. In another five patients (9%), confusion appeared before and persisted after surgery. There was no difference in the incidence of postoperative mental confusion between patients having epidural and general anesthesia (14/28 and 11/29). The absence of a significant difference in the incidence of confusion in these two groups of patients does not exclude the possibility that a more extensive study might have defined the presence of a statistically significant difference.

Our results do not agree with those of Hole et al. (15), who compared patients having elective hip replacement surgery under epidural analgesia or narcotic anesthesia. These authors could not demonstrate that any of their 29 patients operated on under epidural analgesia had signs of postoperative mental deterioration. In comparison, they found seven of 31 patients given a general anesthetic had significant postoperative mental changes. They ascribed the difference between the groups mainly to hypoxemia following general anesthesia. In the present study, confusion following general anesthesia correlated with a significant reduction of arterial oxygen tension values from the pre- to the early postoperative period. In contrast to Hole et al. (15), we found a high incidence of postoperative confusion in patients who had been operated upon under epidural analgesia. Patients with confusion in the epidural group did not have any reduction in arterial oxygen tension postoperatively. Thus, hypoxemia was not the only cause of postoperative confusion among our patients.

Consistent with previous studies comparing regional and general anesthesia, in comparable patients (10,24) spinal anesthesia was associated with a significantly greater intraoperative decrease in arterial blood pressure than halothane or narcotic anesthesia. Although three of our patients developed a stroke after epidural anesthesia, only one of them had a more than 30% reduction in systolic blood pressure. We could find no correlation between the magnitude or duration of hypotension and the incidence of postoperative confusion.

The most important predictor for postoperative mental confusion in the present patient material was regular use of drugs with anticholinergic effects ($P < 0.005$ by multiple regression analysis). Ten of 13 patients who were taking such drugs regularly at the time of admission developed postoperative confusion. More patients were receiving anticholinergic medication in the epidural group at the time of admission than in the halothane group (ten vs three). The incidence of anticholinergic-related confusion was, however, no different between the two anesthetic techniques (eight of ten versus two out of three). When patients on anticholinergic medication were excluded, there was still no difference in the incidence of postoperative confusion between the anesthetic groups. A correlation between plasma anticholinergic levels and postoperative confusion was previously described in a small number of patients having open heart surgery (16). Furthermore, there is a poor correlation between drug dosage and plasma anticholinergic levels (25). Low doses could result in high plasma levels in individual patients. Elderly patients have decreased central nervous system (CNS) concentrations of cholinergic fibers in their brain (26) and may thus be more susceptible to low-dose anticholinergic medication. Ten patients in our study had mental depression on admission. Eight of them, all taking drugs with anticholinergic side effects, developed postoperative confusion ($P < 0.0005$). Patients with mental depression are known to have lower levels of CNS neurotransmitter substances, which might predispose to confusion (27). Accordingly, it is impossible to distinguish between depression per se and associated medication as the dominant risk factor for the development of confusion.

The low 1-yr mortality (7%) in our study is comparable to that found in other studies of similar patients (28,29). There was no significant difference in the incidence of any postoperative complications in the two anesthetic groups (Table 2). However, confused patients were represented to a substantially higher degree among those who developed postoperative complications. Urinary tract infection in the postoperative period occurred in 16 patients, 14 of whom were confused. Incontinence was seen in 11 patients; of these, ten were confused. Pressure sores developed in eight confused patients. Postoperative mental confusion resulted in delayed mobilization and three- to four-fold longer durations of hospitalization. Confusion following surgery for hip fractures is thus associated not only with undesirable humanitarian but also undesirable economic consequences.

In our study, we have defined early postoperative hypoxemia and preoperative regular use of drugs with anticholinergic activity as two important contributing factors associated with postoperative mental confusion. Hypoxemia, if recognized, may be easily avoided. Although cholinergic drugs such as physostigmine are effective in producing temporary alertness in patients with anticholinergic drug overdosage (30,31), it remains to be seen whether postoperative confusion can be prevented or reversed by therapy along these lines.

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Noninvasive Measurement of Gastric Emptying in Obstetric Patients

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O'SULLIVAN GM, SUTTON AJ, THOMPSON SA, CARRIE LE, BULLINGHAM RE. Noninvasive measurement of gastric emptying in obstetric patients. Anesth Analg 1987;66:505–11.

An epigastric impedance technique was used to measure gastric emptying in nonpregnant women, women in the third trimester of pregnancy, and women within 60 min of delivery. The basis of the technique is the increase in epigastric impedance after the ingestion of a nonionic fluid. The subsequent decline in impedance is used as a measure of gastric emptying. The impedance epigastrograph used consisted of a four-electrode array (two source, two detector) that was applied over the epigastrium. The method was sufficiently sensitive to measure the effects of pregnancy, labor, and narcotics on gastric emptying. There was no difference in the rate of gastric emptying between pregnant and nonpregnant females. Labor appeared to cause a significant delay in gastric emptying; the mean ± SEM time taken for the gastric volume to decrease to 50% ($T_{0.5}$) was 7.2 ± 0.6 min during pregnancy and 13.0 ± 1.9 min in the immediate postpartum period. However, the principal factor associated with the delay in gastric emptying in the group studied within 60 min of delivery was probably the use of meperidine and promethazine, because there was a significant difference ($P < 0.05$) between subjects who received meperidine and promethazine during labor and those in another group who had received either no analgesia or extradural analgesia, the $T_{0.5}$ values for the two groups being 18.2 ± 4.0 and 10.3 ± 1.4 min, respectively.

Key Words: ANESTHESIA—obstetric. GASTROINTESTINAL TRACT—stomach. MEASUREMENT TECHNIQUES—epigastrography.

Gastric factors in determining the risk of developing Mendelson's syndrome (1) include a low intragastric pH and a large residual volume. Because gastric emptying is believed to be significantly delayed during labor, oral intake during labor is generally discouraged. Although there have been significant advances in the methods of assessment of gastrointestinal secretion, motility, electrical activity, and peptides, these techniques have not been applied during pregnancy. A reassessment of gastric activity during pregnancy and labor might permit a more rational approach to the use of oral hydration or drug administration in parturients.

Many factors mitigate against the easy assessment of gastric emptying during pregnancy and labor. X-ray and scintigraphic techniques are ethically unjustifiable in pregnant women. Dye dilution and large volume serial meal techniques require nasogastric intubation, and in the past such studies during pregnancy have resulted in poor patient compliance (2,3), in addition to which nasogastric intubation might itself alter the dynamics of gastric secretion and emptying. Potentially ideal methods of measuring gastric emptying during pregnancy would be simple, safe, and noninvasive. Although the relatively simple paracetamol absorption method has been applied during labor (4), it is only an indirect method of measurement that depends on the complete absorption of paracetamol from the upper small intestine, thus leaving gastric emptying to determine the rate of absorption. Of the newer direct, noninvasive techniques for measuring gastric emptying, real time ultrasound (5) and impedance techniques (6) seem appropriate for use during pregnancy. Both techniques require the administration of a relatively large volume of liquid so that neither is ideal for studies during labor, but

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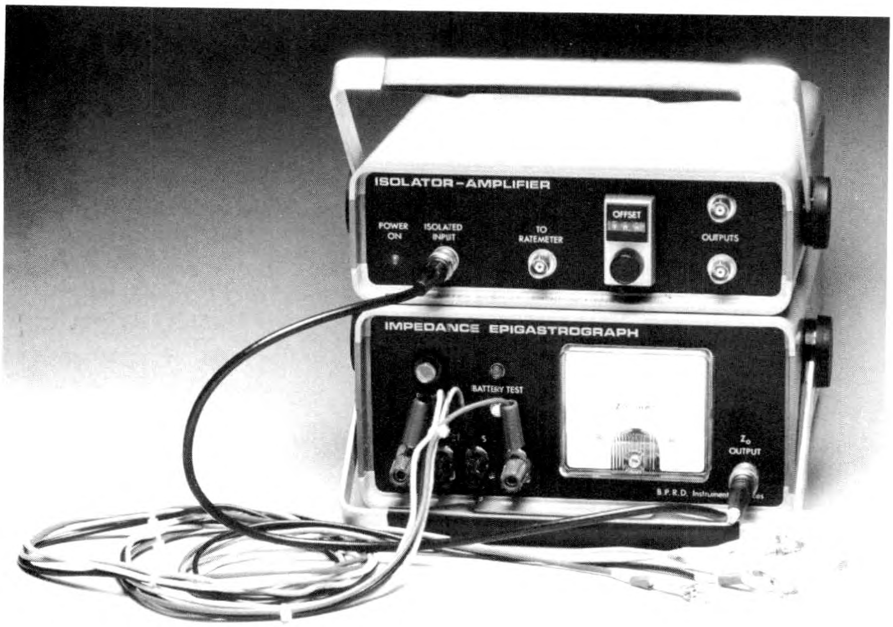

Figure 1. Equipment used to measure gastric emptying by the impedance technique.

the assessment of the rate of emptying immediately after delivery of the fetus and placenta might be a suitable alternative.

This study evaluates the use of a noninvasive epigastric impedance technique for measuring gastric emptying during the third trimester of pregnancy and immediately postpartum.

Materials and Methods

The study was approved by the local Research and Ethics Committee and all the women gave informed consent. An epigastric impedance technique was used to measure gastric emptying in three groups of women: 1) 15 nonpregnant controls of child-bearing age, 2) 30 women late in the third trimester of pregnancy, and 3) 23 women within 60 min of delivery. No patient had a history of gastrointestinal disease. In the pregnant patients heartburn was not a criterion for exclusion. Labor had been induced in all subjects studied immediately after delivery. Indications for induction included postterm pregnancies, intrauterine growth retardation, and increased blood pressure at or near term. In 14 patients prostaglandin pessaries (PGE_2 in a glyceride based pessary) were used on the morning of induction to aid dilation of the cervix. After amniotomy labor was augmented with intravenous oxytocin if required. The women in groups 1 and 2 fasted for at least 4 hr before the study whereas the women studied after delivery had a light breakfast on the morning of induction and sips of water during labor. In the latter patients the study was performed within 60 min of the delivery of the baby and the placenta. Analgesia of the patient's choice (which included extradural 0.5% bupivacaine plain, intramuscular meperidine, 100 mg, and 25 mg promethazine or premixed nitrous oxide–oxygen) was used as required during labor.

Epigastric Impedance Technique

Figure 1 illustrates the equipment used. Adhesive silver/silver chloride electrodes (Hewlett Packard, type 14445A) were positioned as follows: an input electrode was placed one third of the distance along a line (XU) from the xiphisternum to the centre of the umbilicus (XU/3), a recording electrode was placed an equal distance further caudally (2XU/3) and laterally. On the back a recording electrode position remained at the XU/3 level but XU/2 to the left of the midline while an input electrode level was at 2XU/3 and XU/6 to the left (Fig. 2). These points were marked with a tape measure while the subjects were standing. Occasionally adjustments of the measurements for positioning the electrodes were required in pregnant women with very large abdomens, and in these women the positions were judged by eye.

A constant 2mA, 100 KHz AC current was applied through the pair of input electrodes while the other pair recorded changes in voltage. The studies were performed with the patients sitting and, to prevent artefacts, speaking and excessive movements were forbidden during the study. Circuitry is described in Figure 3 and includes isolation circuitry for patient

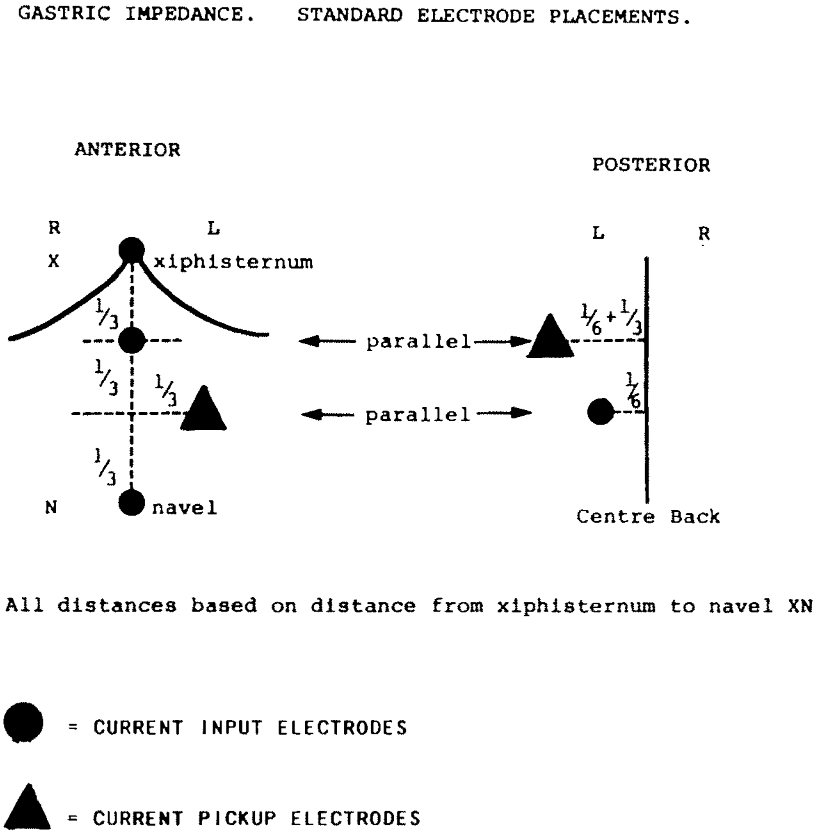
GASTRIC IMPEDANCE. STANDARD ELECTRODE PLACEMENTS.
ANTERIOR
POSTERIOR
R
L
L
R
X
xiphisternum
1/3
1/3
1/3
1/3
N
navel
parallel
parallel
1/6+1/3
1/6
Centre Back
All distances based on distance from xiphisternum to navel XN
= CURRENT INPUT ELECTRODES
= CURRENT PICKUP ELECTRODES

Figure 2. Position of electrodes for measurement of gastric emptying by the impedance technique.

safety. Low pass filtering (−3dB at 0.1 Hz) excluded cardiac, but not respiratory, signal interference. An offset voltage control allowed for differences in basal body impedances. The output signal was recorded on a Bryans 28000 flatbed chart recorder with a paper speed of 5 mm/min.

The subjects drank 500 ml of water or diluted orange concentrate at room temperature over a 2 min period, although in some of the postpartum patients up to 3 min was required to drink the fluid. The deflection height of gastric filling above the baseline was measured by ruler and designated 100%. The times taken to reduce to 70%, 50%, and 30% of the original deflection were calculated (Fig. 4) giving values for $T_{0.7}$, $T_{0.5}$, and $T_{0.3}$ respectively. A one-way analysis of variance followed by Duncan's multiple range tests was used to compare the results of the three groups.

Results

Mean ± SEM age, weight, and height of the volunteers and the women in the third trimester of pregnancy were 28.6 ± 1.1 yr, 58.6 ± 2.0 kg, and 1.7 ± 0.01 m, and 26.3 ± 1.1 yr, 74.5 ± 2.0 kg, and 1.62 ± 0.01 m, respectively. Mean age and height of the women studied postpartum were 25.6 ± 1.0 yr and 1.61 ± 0.01 m.

The stomach could not be located and thus recording of emptying was not possible in 14 subjects; this included one volunteer, ten women in the third trimester group, and three women in the postpartum group. In two women in the pregnant group and one each in both the nonpregnant and the postpartum groups the initial change in impedance after drinking the liquid was not followed by a subsequent return to the baseline. In the postpartum group two patients vomited shortly after drinking the water and the recordings from two other patients were not suitable for analysis due to the presence of artifact caused by excessive patient movement (Fig. 5). After these exclusions there were 13 patients in the nonpregnant group, 18 patients in the third trimester group, and 15 patients in the postpartum group.

Table 1 gives the times to 70%, 50%, and 30% emptying of the stomach in the three groups of subjects. There was a statistically significant difference ($P < 0.05$) between the emptying times of the patients studied immediately after delivery and the other two groups. When the women studied postpartum were divided into groups according to the analgesia used during labor, the women in the group who had re-

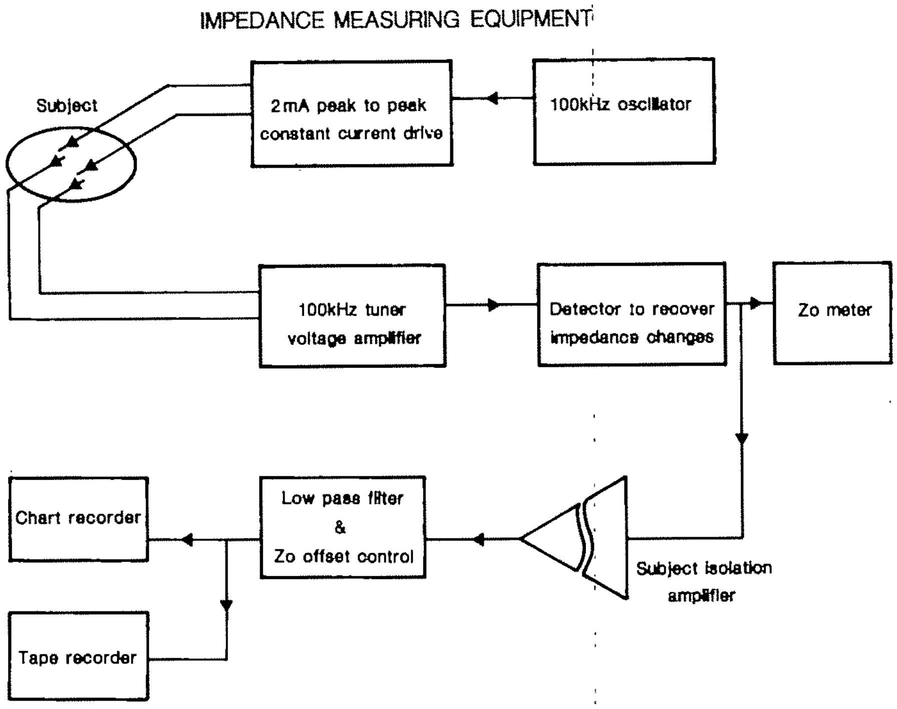
IMPEDANCE MEASURING EQUIPMENT
Subject
2mA peak to peak constant current drive
100kHz oscillator
100kHz tuner voltage amplifier
Detector to recover impedance changes
Zo meter
Chart recorder
Low pass filter & Zo offset control
Subject isolation amplifier
Tape recorder

Figure 3. Circuitry of the impedance measuring equipment.

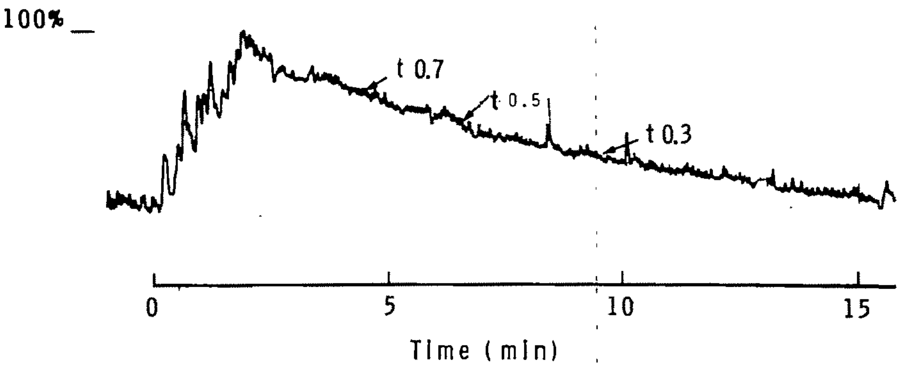

Figure 4. Change in epigastric impedance after the administration of 500 ml of water to a fasting nonpregnant patient. $T_{0.7}$, $T_{0.5}$, and $T_{0.3}$ are the points at which the epigastric impedance had decreased to 70%, 50% and 30% of the maximum deflection.

ceived meperidine and promethazine had a slower rate of gastric emptying than those in the group who received either no analgesia or extradural analgesia (Table 2, Fig. 6). The subjects given meperidine and promethazine also had a significantly longer ($P < 0.05$) emptying time than the third trimester and volunteer subjects. The mean ± SEM time between the administration of the meperidine and promethazine and the commencement of the study was 126 ± 21.1 min. Although the emptying times of the subjects in labor who had not received meperidine and promethazine were slightly longer than in the volunteer and pregnant groups, this difference was not statistically significant.

Discussion

The epigastric impedance method of measuring gastric emptying is a novel application of a well known technique used to monitor respiratory volumes and cardiac contractility. In principle the application to gastric volume measurement requires no more than a caudal adjustment of the electrode position. Measurements of gastric emptying using this epigastric impedance technique correlate significantly with dye dilution (7) and scintigraphic techniques (6). Epigastric impedance is particularly suitable during pregnancy as it is noninvasive and precludes the use of x-rays or radioactive materials. Furthermore, naso-

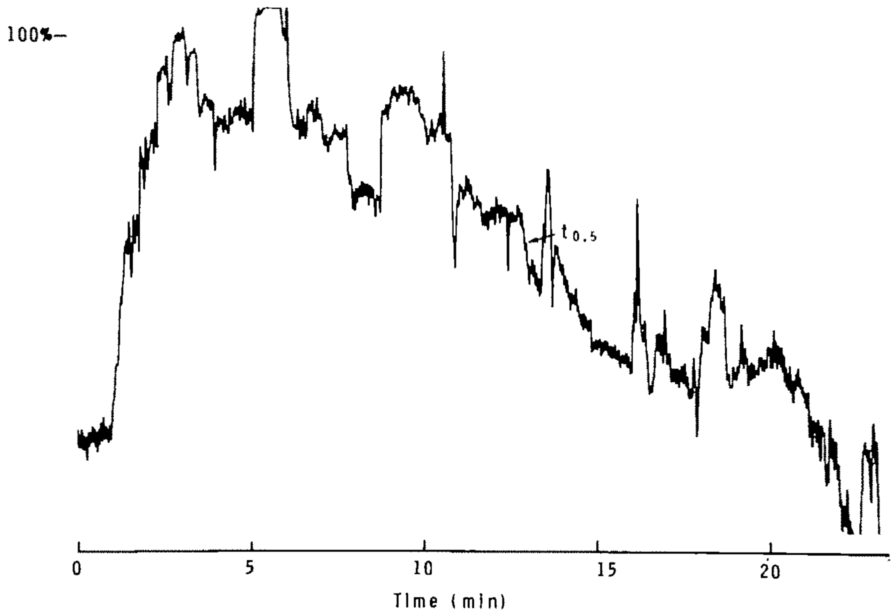

Figure 5. Change in epigastric impedance in a patient studied immediately postpartum. The artifacts on this recording were caused by patient movements.

Table 1. Values for the 70%, 50%, and 30% Gastric Emptying Times of 500 ml of Water in Female Volunteers, Women in the Third Trimester of Pregnancy, and Women in the Immediate Postpartum Period

	Nonpregnant	Third trimester	Postpartum
Number of subjects	15	30	23
Number of analyzable studies	13	18	15
$T_{0.7}$ (min)^a	5.2 ± 0.6	4.4 ± 0.5	8.8 ± 1.6^b
$T_{0.5}$ (min)^a	8.3 ± 0.9	7.2 ± 0.6	13.0 ± 1.9^b
$T_{0.3}$ (min)^a	11.1 ± 1.3	9.8 ± 0.8	15.8 ± 2.3^c

[a] Values are mean ± SEM.

[b] Significant difference ($P < 0.05$) between subjects immediately postpartum and the other two groups.

[c] Significant difference ($P < 0.05$) between subjects immediately postpartum and the women in the third trimester of pregnancy.

Table 2. Gastric Emptying Times in the Postpartum Subjects Who Had and Had Not Received Opiate Analgesia

	No analgesia or extradural analgesia	Meperidine and promethazine	P value
Number of subjects	15	8	
Number of analyzable studies	10	5	
$T_{0.7}$ (min)^a	6.6 ± 1.4	13.1 ± 3.0	<0.05
$T_{0.5}$ (min)^a	10.3 ± 1.4	18.2 ± 4.0	<0.05
$T_{0.3}$ (min)^a	12.9 ± 1.5	21.8 ± 5.6	<0.05

[a] Values are mean ± SEM.

gastric intubation is avoided, thus overcoming any mechanical or psychological stimulation associated with this technique.

The impedance epigastrograph used in this study was a prototype in which a standard four-electrode array (two source, two detector) was applied over the epigastrium (8). Silver/silver chloride electrodes were used because of their prolonged and stable electrical contact. The positioning of the four-electrode array, described above, is capable of detecting impedance changes consequent upon gastric filling in the vast majority of subjects. However, the stomach rotates rostrally in obese subjects and adjustments in the position of the electrodes are necessary to detect gastric filling in such individuals (9). A similar rostral displacement may occur in pregnancy and could account for the lack of impedance changes in some of the women late in the third trimester of pregnancy. Perhaps if the number of electrodes were increased, thereby increasing the area of epigastrium evaluated, the number of subjects in whom the stomach is "missed" would be reduced. Impedance topography, developed by Brown et al., has a ring of electrodes around the trunk (10) and although this system requires complex and expensive equipment to process the impedance changes, gastric filling is invariably detected.

The simplicity and portability of the impedance epigastrograph, although an advantage in terms of clinical applications, renders it susceptible to movement-induced artefacts. Minor limb movements cause only transient changes in impedance traces, but deep respirations and changes in body position can significantly and permanently alter the baseline impedance level and thus may invalidate a recording. In general,

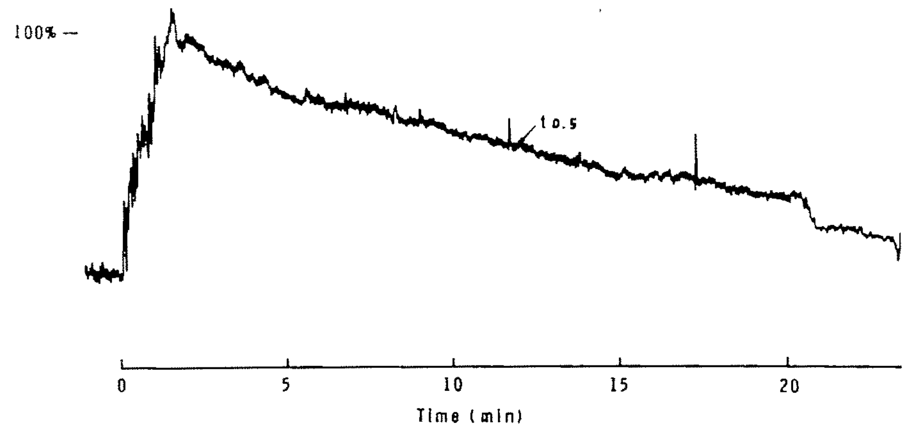

Figure 6. Change in epigastric impedance in a postpartum subject who had received 100 mg meperidine and 25 mg promethazine during labor.

excessive movements by the patients were not a problem except in the postdelivery studies when factors such as a painful episiotomy site made prolonged sitting uncomfortable. A further limitation of the method at present is the relatively large volume of fluid required to produce deflections suitable for quantitative analysis. This precluded use of the technique during labor and thus, as a compromise, women in the immediate postpartum period were studied.

The results of this study indicate that pregnancy does not significantly alter the emptying time of a large volume of liquid from the stomach. Women in the third trimester had half emptying times similar to those in the nonpregnant control group. The women studied in the immediate postpartum period had a significantly slower rate of emptying than both the pregnant and nonpregnant women, which suggests that labor is probably associated with a slowing of gastric emptying. However, because of the intrinsic complexity of labor and the use of a wide variety of pharmacologic agents during labor, the interrelationships of the influences on gastric emptying occurring at this time cannot be easily defined. In this study, because ethical considerations required that women could only be studied after delivery, factors such as delivery or the use of forceps may also have influenced the rate of gastric emptying. Of the drugs commonly used during labor it is the opiate analgesics that are known to have the most marked effect on the smooth muscle of the gastrointestinal tract (11), and in this study the subjects who had received meperidine and promethazine in labor had a significantly slower rate of gastric emptying, the mean $T_{0.5}$ being 18.2 min compared with a mean $T_{0.5}$ of 10.3 min for the group who had received either extradural or no analgesia during labor. The women who did not have meperidine and promethazine during labor had rates of gastric emptying similar to both nonpregnant controls and women in the third trimester of pregnancy.

Previous studies on gastric emptying during pregnancy and labor generally support the present findings. Hunt and Murray showed that pregnancy had no effect on the volume of gastric contents remaining in the stomach 10 min after the ingestion of a 750 ml water or saline test "meal" (12). La Salvia and Steffen measured the rate of clearance of a thin barium mixture from the stomach in women in late pregnancy and during labor. Pregnancy was not found to alter gastric emptying, but the administration of 100 mg meperidine and 0.4 mg scopolamine to both groups caused a more marked delay in gastric emptying during labor than in the third trimester, indicating an effect of labor in addition to the effect of the drugs (13). In another x-ray study of ten women in labor who had received no analgesia, two women had delayed evacuation of barium from the stomach (14), although in a similar study in which the use of analgesia was not documented only one patient in a series of 12 showed any delay of gastric emptying (15). Similar results were seen when the rate of gastric emptying was estimated indirectly from the kinetics of absorption of orally administered paracetamol (4,16). One study showed that the mean plasma paracetamol level 45 min after ingestion was 18.0 μg/ml in early labor, 12.0 μg/ml during established labor, and 1.9 μg/ml in subjects who received opiates during labor. Because paracetamol is mainly absorbed from the upper small intestine the delay in absorption indirectly reflects a delay in gastric emptying.

Using a double sampling, dye-dilution method (17) Davison et al. found no change in the half-life of emptying nor in the mean volume of gastric contents 30 min after the start of the study in women in late pregnancy. However, there was a delay in the time until the stomach was totally evacuated. During labor both the total and half-life of emptying were delayed in women who had received no analgesics, and in addition, the pattern of emptying was altered (18). These latter results do not necessarily contradict the previous studies but probably reflect the greater number of parameters used to evaluate gastric emptying. Howard and Sharp, who also used the double sampling, dye-dilution technique, demonstrated that 10 mg intramuscular metoclopramide accelerates gastric emptying during labor, but in their study there was no control group and no distinction was made between parturients who had and had not received meperidine (19).

In this study the rate of gastric emptying in the postpartum patients was significantly delayed by the administration of pethidine and promethazine. Because previous studies of gastric emptying during labor indicate that labor alone causes a minimal delay in gastric emptying that is only prolonged by the use of opiate analgesia (4) this suggests that some fluid could be taken orally during normal labor. However, as the impedance technique does not always permit the measurement of the rate of emptying of the final 20–30% of the administered fluid, this present study cannot definitively answer the question of the appropriateness of oral intake. The delay in gastric emptying that appeared to be associated with the use of meperidine and promethazine in this study means that women given meperidine during labor should have their oral intake restricted. This conclusion is supported by a study (20) in which the volume of gastric contents was measured both in women undergoing elective cesarean section and in women in labor requiring cesarean section. The largest mean intragastric volumes (122.3 ± 13.2 ml) were found in women who had received meperidine during labor, whereas the mean ± SEM volume in those who had received no analgesia during labor was 67.9 ± 9.6 ml.

In conclusion, a simple, noninvasive epigastric impedance technique is sufficiently sensitive to elucidate the effects of pregnancy and labor on gastric emptying and thus is suitable for the assessment of gastric emptying during pregnancy and, more generally, in the perioperative period.

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Potentiation of Atracurium Toxicity in Isolated Rat Hepatocytes by Inhibition of its Hydrolytic Degradation Pathway

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NIGROVIC V, KLAUNIG JE, SMITH SL, SCHULTZ NE. Potentiation of atracurium toxicity in isolated rat hepatocytes by inhibition of its hydrolytic degradation pathway. Anesth Analg 1987;66:512–6.

This study tested the hypothesis that the esters of acrylic acid might be responsible for the previously observed cytotoxic effect of atracurium. Rats were pretreated with triorthotolyl phosphate (TOTP), an inhibitor of the hydrolytic degradation of atracurium. Because hydrolysis of acrylates is also inhibited by TOTP and because the hydrolysis represents a detoxification pathway for these esters, we postulated that the leak of lactic dehydrogenase (LDH) induced by atracurium would be enhanced in hepatocytes harvested from rats pretreated with TOTP. Hepatocytes isolated from rats previcusly treated with TOTP (25 or 50 mg/kg intraperitoneally, 20 hr before induced death) were incubated for 4 hr in the absence of muscle relaxants or in the presence of either atracurium (0.008–0.8 mM) or metocurine (0.015–0.85 mM). Atracurium produced a concentration-dependent leakage of LDH. The leakage out of cells obtained from TOTP-pretreated rats was greater than was the leakage out of hepatocytes harvested from animals pretreated only with corn oil (a vehicle for TOTP). Metocurine did not produce a leak of LDH. It is concluded that the LDH leakage was produced by ester-type products of atracurium degradation. Acrylates appear to be the toxic agent.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium.

The generation of esters of acrylic acid from atracurium in vivo has raised a question of their possible undesired effects (1). This concern was based on the high chemical reactivity of acrylates toward nucleophiles. This suspicion was recently substantiated (2) by demonstrating that atracurium, when incubated with rat hepatocytes for 4 hr, produced a concentration-dependent leakage of lactic dehydrogenase (LDH). The study of Nigrovic et al. did not elucidate the mechanism leading to this cytotoxic effect. Although other metabolic products were considered, acrylates were suggested as the likely toxic agents. The present study was conducted to narrow the choice among the candidates possibly responsible for the enzyme leak. We reasoned that the postulated toxic effects of acrylates would become more evident if Hofmann elimination was made the dominant degradation pathway of atracurium. To accomplish this goal, we pretreated rats with triorthotolyl phosphate (TOTP) to inhibit enzyme-catalyzed hydrolysis of atracurium (3). The decreased rate of enzyme-catalyzed hydrolysis might be expected to leave more atracurium to be degraded by Hofmann elimination and hence, to lead to an increased formation of acrylates. The rate of hydrolysis of acrylate esters is also expected to be diminished by this treatment (4). As a working hypothesis, we postulated that the inhibition of enzyme-catalyzed hydrolysis would increase the leakage of LDH from hepatocytes incubated in the presence of atracurium. In some experiments metocurine was used as a negative control. This relaxant was selected because it is a bis-quaternary compound chemically similar to atracurium (5) but is not susceptible to either Hofmann elimination or ester hydrolysis.

Methods

Male Wistar rats (70–170 g body weight) were treated with TOTP (25 or 50 mg/kg intraperitoneally, diluted in corn oil, total injected volume 2 ml/kg) 20 hr before their liver cells were harvested. Control rats were treated with only corn oil. Isolation and culture of the hepatocytes were performed as previously described (2) using methods modified from Klaunig et al. (6,7).

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Briefly, in rats anesthetized with sodium pentobarbital (65 mg/kg intraperitoneally), the abdominal cavity was surgically opened and the liver perfused in situ via the portal vein in two stages. Perfusion with Hank's solution was carried out first and was followed by perfusion with L-15 medium containing collagenase (type IV). Viability of the isolated cells was estimated by the trypan blue exclusion test. Only isolates with viability >85% were used in subsequent studies. The cells were plated onto 60-mm culture dishes (10^6 cells per dish) in 3-ml L-15 medium supplemented with gentamicin (25 μg/ml), fetal bovine serum (10%), glucose (1 mg/ml), and dexamethasone (1×10^{-6} M). The dishes were incubated for 2.5 hr (36.5°C, air atmosphere, 100% relative humidity) to allow the cells to attach to plastic dishes. After attachment, the medium was discarded and the attached cells were washed once with L-15 medium. Fresh L-15 medium was then added. Commercial solutions of atracurium or metocurine were added (always <500 μl) to achieve the desired concentration in a total incubation volume of 5 ml. The final concentrations of the relaxants were identical to those in the previous study (4). In every experiment each concentration of each muscle relaxant was tested in three dishes. Additional culture dishes containing hepatocytes were included in each experiment; one set of three dishes served to determine the leak of LDH in the absence of relaxants, and the other set was used to measure the total amount of LDH in the culture medium after the lysis of cells with Triton X-100 (50 μl). All incubations were carried out in an incubator (36.5°C, air atmosphere, 100% relative humidity) for 4 hr after the addition of the relaxants. At the end of incubation the medium was removed and filtered. The activity of LDH in the medium was determined spectrophotometrically (Beckman Multistat Autoanalyzer). A total of 15 experiments were performed; six rats were pretreated with oil only, three with the lower dose of TOTP (25 mg/kg) and six with the higher dose (50 mg/kg). The sources of the chemicals were: TOTP from Eastman Kodak Co., Rochester, NY; atracurium besylate (Tracrium) from Burroughs Wellcome Co., Research Triangle Park, NC; metocurine iodide (Metubine) from Eli Lilly and Co., Indianapolis, IN. Other chemicals were purchased from Sigma Chemical Co., St. Louis, MO.

The net leak of LDH produced by a relaxant was defined as

$$\frac{\begin{array}{c}\text{(LDH in treated dish}\\ -\text{ LDH in untreated dishes)}\end{array}}{\text{(maximal LDH } - \text{ LDH in cell-free medium)}} \times 100, \qquad (1)$$

where LDH refers to the LDH activity in the medium collected from a dish exposed to a relaxant ("treated dish") and the average of LDH activity from three control dishes ("untreated dishes"). The denominator in Equation 1 represents the total LDH activity that was present in hepatocytes incubated in a single dish. This value was calculated by subtracting the LDH activity in the cell-free medium ("LDH in cell-free medium") from the mean LDH activity in culture media collected from three dishes with cells lyzed with Triton X-100 ("Maximal LDH"). The lower limit for the net leak of LDH is 0%, if the relaxant did not increase the leakage of LDH above that observed in untreated dishes. The higher limit is

$$\frac{\text{(maximal LDH } - \text{ LDH in untreated dishes)}}{\text{(maximal LDH } - \text{ LDH in cell-free medium)}} \times 100, \qquad (2)$$

if the relaxant caused a release of all intracellular enzyme. A two-way analysis of variance was performed on the atracurium data obtained from rats pretreated with corn oil and the higher dose of TOTP (50 mg/kg) to estimate separately the influence of the two main factors, namely, the concentration of atracurium and the treatment with TOTP, as well as their interaction. Data are presented as mean ± SEM.

Table 1. Net LDH Leak during the Incubation of Rat Hepatocytes with Metocurine

	TOTP (mg/kg intraperitoneally)	
Metocurine (M $^{-6}$)	25[a] (n = 3)	50[b] (n = 6)
11.9	0.35	−0.46 ± 1.34
35.3	0.31	−0.61 ± 1.17
111.1	0.14	+0.51 ± 1.27
353	0.30	−0.08 ± 1.35
851	−1.01	−2.13 ± 1.16

[a] Values given as percentage. Because of the small number of experiments only the mean values are presented.

[b] Values given as percentage.

Results

The addition of metocurine or atracurium to culture media did not alter either the hydrogen ion activity of the culture medium (pH 7.4) or the measurement of LDH activity in the medium (data not presented).

Leakage of LDH from hepatocytes incubated in plain culture medium, that is, when no relaxants were present, was independent of the TOTP dose. On the average, 10.1 ± 1.0 and 9.9 ± 1.0% of the total intracellular LDH leaked out during the 4-hr incubation period from untreated hepatocytes harvested from six rats pretreated with oil and nine pretreated with TOTP, respectively. According to Equation 2, the leakage of LDH from untreated hepatocytes sets the higher

Table 2. Net LDH Leak during the Incubation of Rat Hepatocytes with Atracurium

Atracurium (M^{-6})	TOTP (mg/kg intraperitoneally) 0[a] $(n = 6)$	25[b] $(n = 3)$	50[a] $(n = 6)$
8.1	−0.44 ± 0.56	3.47	3.52 ± 0.53
25.5	1.10 ± 0.34	8.59	7.60 ± 0.60
80.6	4.12 ± 0.90	14.97	16.03 ± 1.16
255	10.78 ± 1.99	30.1	51.7 ± 2.2
439	20.0 ± 2.7	53.0	74.2 ± 3.3
623	32.8 ± 2.3	71.0	75.5 ± 3.3
807	47.1 ± 2.3	81.5	84.9 ± 2.7

[a] Values given as percentage.

[b] Values given as percentage. Because of the small number of experiments only the mean values are presented.

limit for the net leak of LDH induced by a relaxant to approximately 90%.

Incubation of hepatocytes with various concentrations of metocurine did not produce a net leak of LDH (the values do not differ from 0%). The findings for both doses of TOTP were similar (Table 1).

In contrast (Table 2), the presence of atracurium in the culture medium resulted in a net leak of LDH ($P \ll 0.01$). Each concentration of atracurium, except the lowest one in rats pretreated only with corn oil, produced a positive net leak of LDH. The leak was greater with higher concentrations of atracurium ($P \ll 0.01$). Pretreatment of rats with the higher dose of TOTP further increased the net leak of LDH ($P \ll 0.01$). Interaction between the effects of atracurium and those of the treatment with TOTP was highly significant ($P \ll 0.01$). The smaller dose of TOTP, tested in only three rats, produced results similar to those produced by the larger dose. No statistical analysis was performed on these data because of the small number of animals studied.

Discussion

Reports in the literature substantiate the two basic premises of our study. First, a leakage of an intracellular enzyme is an appropriate quantitative expression of injury to the isolated cells in culture. The leakage is due to damage of the plasma membrane and the magnitude of the leak is proportional to the fraction of injured cells. Cytoplasmic LDH is deemed a good marker of cytotoxicity (8,9). Second, the electrophilic character of the esters of acrylic acid is believed to be responsible for their reactivity toward endogenous nucleophiles (4,10). The conjugated bond in the parent acid is less reactive and the acid itself is less toxic (10,11). Urinary excretion of acrylates as derivatives of mercapturic acid is an additional indication of an antecedent in vivo interaction with tissue sulfhydryl compounds, specifically glutathione (11). Hydrolysis of the acrylate esters by carboxylesterase represents a detoxification pathway (4). Consequently, inhibition of carboxylesterase by TOTP is expected to preserve acrylates and hence, enhance their toxicity. Except for this effect, the administration of TOTP was free of acute adverse effects in the treated rats (4).

The results of the present study agree with an earlier report (2) that showed that the commercial preparation of atracurium produces a net leak of LDH from cultured rat hepatocytes and the commercial preparation of metocurine does not. In both studies the net leak of LDH increased as the concentration of atracurium in the incubation medium increased, although all experimental points obtained from rats pretreated with corn oil (this study) lie below the corresponding points obtained from rats not pretreated (2). The reason for this difference is not apparent.

The effect of pretreating rats with TOTP on the leakage of LDH will be considered separately for hepatocytes incubated in a) the absence of muscle relaxants, b) the presence of metocurine, and c) the presence of atracurium.

a) As reported earlier, the leakage of LDH from hepatocytes incubated without muscle relaxants was not dependent on the dose of TOTP (0, 25 or 50 mg/kg intraperitoneally). We conclude that the treatment with TOTP did not influence the viability of the isolated rat hepatocytes cultured in plain medium. Although the doses of TOTP selected for the present study were smaller than those used by the other investigators, either dose of TOTP was sufficient to establish a marked though incomplete inhibition of the plasma and liver carboxylesterase in rats (4).

b) Metocurine (0.012–0.85 mM) did not produce a net leak of LDH out of hepatocytes isolated either from rats pretreated with TOTP (Table 1) or from untreated rats (2). Therefore, a nonspecific cytotoxic effect of bis-quaternary muscle relaxants on the liver cells isolated from untreated or TOTP-treated rats may be excluded.

c) The net leak of LDH produced by atracurium (0.008–0.8 mM) was higher if the hepatocytes were harvested from TOTP-pretreated rats than if the cells were obtained from rats pretreated with the vehicle only. The effect of TOTP pretreatment was more pronounced for the higher concentrations of atracurium.

The results (Tables 1 and 2) support the working hypothesis and demonstrate that the noxious species could have been either an ester added to the culture medium or an ester formed in the medium during the incubation. Atracurium itself would fit into the first category and acrylates into the second.

is no reason to suspect a toxic biochemical interaction between atracurium and cell constituents, we believe that the parent drug may be excluded from further considerations. Acrylates, on the other hand, are an electrophilic species showing high reactivity toward nucleophiles, and should be considered. Logically, laudanosine should also be considered because it is generated concomitantly and in equimolar amounts with acrylates. However, the chemical structure of laudanosine does not reveal any reason to expect toxic interaction with cellular constituents, and hence, laudanosine will be excluded from further considerations.

Hydrolysis of acrylate esters (methyl, ethyl, and butyl) was previously demonstrated in vitro with tissue homogenates (10). The spontaneous reaction of ethyl acrylate with glutathione in vitro was greatly enhanced by enzyme(s) present in the soluble fraction from rat liver. Acrylic acid did not react with sulfhydryl groups (10). Silver and Murphy (4) used TOTP to demonstrate the consequences of a decreased rate of hydrolysis of acrylate esters (methyl and ethyl) in vivo: an enhanced depletion of nonprotein sulfhydryl groups in various tissues and an increased mortality of rats exposed to inhalation of the esters. Inhibition of the hydrolytic detoxification of acrylates by TOTP redirected the detoxification toward the other pathway, namely, the conjugation to glutathione and formation of mercapturic acid (11). On the basis of these reports, we propose that glutathione may act as a scavenger for acrylates generated in vivo from atracurium. Only after the stores of glutathione are depleted will the offending reactive intermediate cause functional, and perhaps morphologic, damage. Hence, it is not surprising that in the present experiments the cytotoxicity of the lower concentrations of atracurium was only slightly enhanced by the TOTP treatment: low concentrations of atracurium produced only a small amount of acrylates that could have been adequately detoxified by the available glutathione or the residual activity of the esterase, or both. Larger amounts of acrylates probably overwhelmed the available stores of glutathione as well as the residual capacity of the esterase for rapid hydrolysis and detoxification.

Treatment of rats with TOTP might have increased the cytotoxicity of atracurium by two mechanisms: first, by increasing the amount of the parent drug available for Hofmann elimination and the generation of acrylates; and second, by reducing the hydrolytic degradation of acrylates and prolonging their sojourn in the biophase. We propose that these two mechanisms are responsible for the augmentation of atracurium-induced LDH leak by the treatment with TOTP. Acrylate metabolites of atracurium, required to verify the proposed hypothesis, were not available either from commercial sources or from the manufacturer of atracurium.

A translation of the toxic concentrations of atracurium into clinically meaningful terms is not possible. First, the relative contributions of Hofmann elimination and ester hydrolysis to the degradation of atracurium in humans are not known. The activity of carboxylesterase in rat serum is higher than in human serum (12). The data on hydrolytic inactivation of atracurium in human plasma in vitro (13,14) do not correspond with the in vitro data on hydrolytic degradation of atracurium (15). Second, concentrations of atracurium in various organs, even if known, would not provide the desired information about the tissue concentration of acrylates. Concentrations of acrylates in plasma and tissues are not known. However, the presence of laudanosine in plasma of patients treated with atracurium (16) proves indirectly that acrylates must have been produced as well. The in vivo fate of acrylates must be known before the issue of their potential toxicity can be resolved.

The contrast between the easily demonstrable toxic effect of atracurium in our experiments in vitro and its remarkable safety in clinical use (17) needs explanation. Several possibilities may be offered. The clinical dose of atracurium is relatively small and the amount of acrylates formed in vivo may be insufficient to cause clinically manifest side effects. In addition, the stores of glutathione might be sufficient to scavenge acrylates produced in the amounts and at the rates encountered in clinical practice. Finally, a minor cellular injury produced by acrylates may be repaired in vivo, whereas similar repair processes in vitro are unlikely.

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Butorphanol Improves CO_2 Response and Ventilation after Fentanyl Anesthesia

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BOWDLE TA, GREICHEN SL, BJURSTROM RL, SCHOENE RB. Butorphanol improves CO_2 response and ventilation after fentanyl anesthesia. Anesth Analg 1987;66:517–22.

We have determined that the mixed agonist-antagonist narcotic, butorphanol, improves CO_2 response and ventilation after fentanyl anesthesia. A tentative dosage range has been established. Twenty-two patients were anesthetized with isoflurane, nitrous oxide, and fentanyl, which was continuously infused throughout the study. Postoperatively three 1-mg doses of butorphanol were administered IV. Blood pressure, heart rate, plasma epinephrine and norepinephrine concentrations, and pain intensity were essentially unchanged after butorphanol. Most of the improvement in breathing occurred after the first 1-mg dose. Mean respiratory rate increased from 7.8 ± 5.0 to 11.0 ± 4.8 min^{-1} ($P \le 0.005$), tidal volume increased from 469 ± 302 to 844 ± 390 ml ($P \le 0.005$), minute ventilation increased from 4.32 ± 2.97 to 8.51 ± 3.14 L/min ($P \le 0.005$), and the slope of the ventilatory response to CO_2 increased from 0.36 ± 0.37 to 0.90 ± 0.80 L·min^{-1}·mm Hg^{-1} ($P \le 0.05$). Resting Pa_{CO_2} decreased from a baseline of 57.8 ± 11.1 to 51.7 ± 5.12 mm Hg ($P \le 0.05$) after the third dose.

Key Words: ANALGESICS—fentanyl, butorphanol. ANTAGONISTS, NARCOTIC—butorphanol. VENTILATION—CO_2 response curves.

The use of potent narcotic agonists as primary anesthetic agents has become quite popular, in part because of the cardiovascular stability that results from combining a substantial dose of narcotic with a small concentration of a potent inhalational agent (with or without N_2O). Depending on the type of narcotic agent used, its dose, and the length and type of surgical procedure, a variable amount of respiratory depression may occur at the conclusion of the operative procedure. Respiratory depression may be mild and require no treatment, or may be severe and require postoperative ventilation or pharmacologic reversal of the narcotic. Naloxone is widely used to antagonize respiratory depression caused by narcotic agonists. Naloxone binds the narcotic receptor without activating it, thereby blocking the effects of the agonist drug. Unfortunately, when used to reverse narcotics, naloxone may cause undesirable adverse effects, such as severe hypertension, cardiac arrhythmias including ventricular fibrillation, and pulmonary edema (1–5). The mechanism of these adverse effects is unknown, but may be related to an increase in sympathetic tone, because when dogs anesthetized with fentanyl, enflurane, and nitrous oxide receive naloxone, catecholamine levels increase (6). Reversal may also be unpleasant for the patient because analgesia may be reversed along with respiratory depression.

Because of the variety of problems associated with naloxone administration, there has been a search for drugs that would reverse the respiratory depressant effects of narcotic anesthetic agents without producing pain or cardiovascular instability. Physostigmine has been used to antagonize respiratory depression caused by morphine, presumably by activating cholinergic pathways in the respiratory control centers of the brain that enhance ventilation (7). Analgesia is preserved, but atropine is required to prevent the systemic cholinergic effects of physostigmine (nausea, vomiting, bradycardia). Nalbuphine, a mixed agonist-antagonist narcotic, antagonizes the respiratory depressant effect of μ-agonists such as fentanyl (8–10) without reversing analgesia. Presumably nalbuphine antagonizes fentanyl at the μ-receptor, whereas nalbuphine κ-receptor agonist activity tends to maintain analgesia (11). However, pain and cardiovascular instability were noted in one study (12), whereas another study found that circulating epinephrine concentrations increased threefold after reversal (10). A

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Table 1. Results[a]

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart rate (1/min)	Epinephrine (pg/ml)	Norepinephrine (pg/ml)	Respiratory rate (1/min)
Baseline	143 (24.6)	72 (14)	84 (21)	663 (781)	697 (549)	7.8 (5.0)
Butorphanol 1 (1 mg)	154 (26.5)	73 (14)	88 (17)	758 (818)	681 (553)	11.0 (4.8)
Butorphanol 2 (1 mg)	158 (27.8)	75 (17)	87 (17)	633 (574)	640 (338)	12.8 (4.4)
Butorphanol 3 (1 mg)	157 (21.5)	77 (16)	84 (16)	770 (770)	594 (442)	11.9 (3.9)
P value	≤0.005, 1 vs baseline ≤0.05, 2,3 vs baseline	—	—	—	—	<0.005, 1,2,3 vs baseline

[a] Means and SD (in parentheses) are shown for the entire group of 22 patients, for baseline conditions, and for the three sequential doses of butorphanol, 1 mg.

[b] Subset of eight of the 22 patients.

recent study (13) found no significant antagonism of morphine-induced respiratory depression by nalbuphine.

Butorphanol is a mixed agonist-antagonist narcotic that shares certain properties with nalbuphine. Animal studies have suggested that butorphanol is a μ-antagonist or partial agonist (14). It nevertheless can produce substantial analgesia, probably because of κ-receptor agonist activity (11,14). Studies in mice suggest that butorphanol would not be a very potent antagonist at the μ-receptor, compared with nalorphine or nalbuphine (15). However, studies of mice may not fully predict the behavior of the drug in the clinical setting. Therefore, we evaluated whether butorphanol antagonizes the effects of fentanyl on respiratory drive and ventilation in humans, and if so, what is the effective dosage range.

Methods

Patients were anesthetized for surgery with isoflurane, nitrous oxide, and fentanyl. Fentanyl infusion was maintained throughout the study to produce a slowly increasing plasma concentration (see Discussion). Postoperatively, respiratory rate, tidal volume, minute ventilation, ventilatory response to CO_2, arterial blood gas tensions, end tidal isoflurane concentration, blood pressure, heart rate, pain intensity, and catecholamine concentrations were measured before and after each of three 1-mg intravenous doses of butorphanol.

Twenty-two patients gave institutionally approved, informed consent. Their mean age was 49.1 ± 15.2 yr; mean weight was 183 ± 37 pounds. Median ASA rating was 2 (range 1–3). All but two patients were men. Operative procedures included orthopedic (15 patients), urologic (4 patients), and lower abdominal general surgery (3 patients). The duration of surgery was 172 min (SD ± 81). Thoracic and upper abdominal operations were excluded to avoid undue influence of the surgical procedure on the patients' postoperative ventilation. No premedication was used. A radial arterial catheter was inserted in all patients. Fentanyl was administered as a 5 μg/kg body weight bolus during induction and by continuous infusion of 3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, beginning immediately after induction. The intraoperative dose of fentanyl was 1268 ± 452 μg. Thiopental adequate to produce unconsciousness (mean dose 285 ± 96, range 125–500 mg) was followed by succinylcholine to facilitate tracheal intubation. Nondepolarizing muscle relaxants were used for defasciculation and for intraoperative relaxation if necessary, and were reversed with edrophonium before the end of the procedure. Nitrous oxide and isoflurane were used as needed to produce optimal anesthetic depth. The inhalation agents were discontinued before the end of the procedures so that isoflurane end tidal concentrations were ≤0.1% before arrival in the recovery room as measured by mass spectrometry (SARA) in the operating room and recovery room. Fentanyl infusion was continued without interruption during transport and in the recovery room until the study was completed. The fentanyl dose in the recovery room was 193 ± 92 μg.

On arrival in the recovery room, 18 patients were awake, extubated, and breathing spontaneously. Oxygen was administered by mask to prevent hypoxia. The following measurements were made before butorphanol administration, and 5 min after each of three sequential IV 1-mg doses of butorphanol (total dose 3 mg): blood pressure, heart rate, plasma epinephrine and norepinephrine, arterial blood gas tensions, end

Tidal volume (ml)	Minute ventilation (L/min)	Slope, CO_2^{b} response (L·min·torr^{-1})	Pa_{CO_2} (mm Hg)	pH (units)	Pa_{O_2} (mm Hg)
469 (302)	4.32 (2.97)	0.36 (0.37)	57.8 (11.1)	7.24 (0.04)	162 (105)
844 (390)	8.51 (3.14)	0.90 (0.80)	55.3 (10.9)	7.26 (0.06)	180 (70)
750 (234)	9.20 (2.35)	0.99 (0.61)	52.4 (8.38)	7.27 (0.06)	161 (73)
749 (244)	8.63 (2.47)	1.06 (0.56)	51.7 (5.12)	7.28 (0.03)	170 (81)
<0.005, 1,2,3 vs baseline	<0.005, 1,2,3 vs baseline	<0.005, 1,2 vs baseline <0.005, 3 vs baseline	≤0.05, 1,3 vs baseline ≤0.01, 2 vs baseline ≤0.05, 2 vs 1	—	—

tidal isoflurane concentration, pain (rated by the patient as none, mild, moderate, or severe), respiratory rate, tidal volume, minute ventilation, and ventilatory response to CO_2, as determined by the Read rebreathing method (16). The time between butorphanol doses was 10–15 min. Four patients were apneic on arrival to the recovery room; they were handled differently, as described under Results.

Measurements of ventilatory responses to CO_2 were made using a breathing circuit with a Validyne Model MC1-3 pneumotach and a Hewlett-Packard 47210A Capnometer interfaced to a Hewlett-Packard 7754B multichannel recorder. There was approximately 275 ml of respiratory dead space in the circuit, including the anesthesia mask. Spirometric data are reported at BTPS. Carbon dioxide response testing was carried out using the Read rebreathing technique with 7% CO_2 and 40% O_2 (16). The slope of the CO_2 response curve was determined by linear regression beginning from points when end tidal CO_2 approximated mixed venous CO_2. In some patients CO_2 response data could not be obtained because baseline rest CO_2 was very high, or because of intolerance to severe hypercapnia, as manifested by anxiety, dyspnea, and attempts to remove the anesthesia mask from the face. Data on ventilatory responses to CO_2 were obtained in 8 of the 22 patients.

Arterial blood gas tensions were determined in duplicate in our clinical laboratory. Arterial samples for measurement of catecholamine levels were placed in ice after collection. At the conclusion of sample collection the plasma was separated in a cold centrifuge and frozen at −20°C until analyzed by a HPLC assay in our research laboratory (17).

Statistical comparisons were performed using analysis of variance (ANOVA) and Student's *t*-test. Results are given as the mean ± SD. Where data may not have been normally distributed, nonparametric tests (Wilcoxon rank-sum) were also applied, but results were not different from parametric tests.

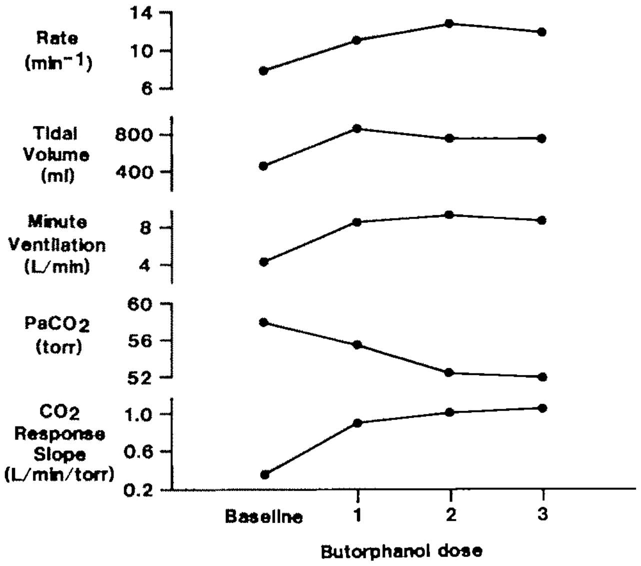

Figure 1. Mean data for respiratory measurements are shown under baseline conditions and after each of three sequential 1-mg doses of butorphanol. Ventilatory response CO_2 data are from eight of the 22 patients.

Results

Results are shown in Table 1 and Figures 1 and 2. End tidal isoflurane concentrations were ≤0.1% on arrival in the recovery room. Eighteen patients were breathing spontaneously and four were asleep, intubated, and apneic on arrival in the recovery room. Baseline spirometric measurements and CO_2 responses could, of course, not be done in the apneic patients. Also data on arterial blood gas tensions in these four patients were excluded because baseline

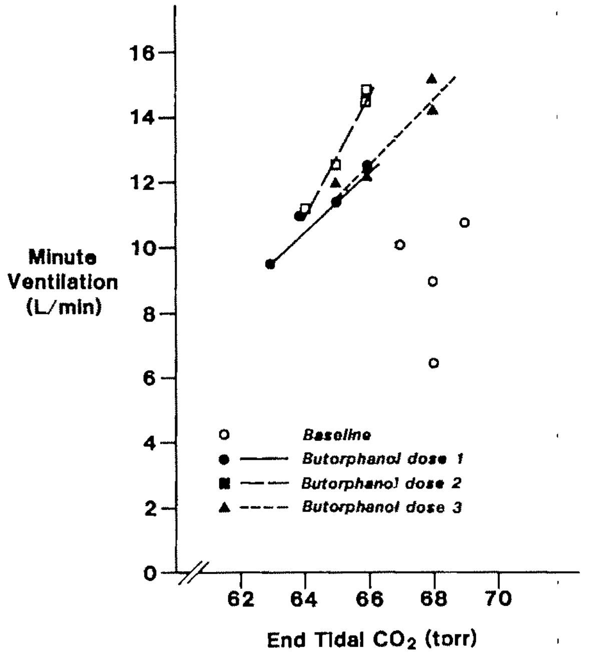

Figure 2. Ventilatory CO_2 response curves (obtained by the method of Read) (16) are shown for an individual patient. Baseline slope (open circles) was 0.31 $L{\cdot}min^{-1}{\cdot}mm\ Hg^{-1}$; this slope was not statistically different from 0 ($P > 0.05$). Slopes after three 1-mg doses of butorphanol were 0.925 (solid circles), 1.83 (squares), and 1.00 $L{\cdot}min^{-1}{\cdot}mm\ Hg^{-1}$ (triangles), respectively.

data were obtained during controlled ventilation. The apneic patients were ventilated with an anesthesia reservoir bag containing oxygen, 100%, and their end tidal CO_2 was maintained in the range of 50–60 mm Hg, which was comparable to the Pa_{CO_2} in spontaneously ventilating patients. Butorphanol, 1 mg was then administered, resulting in the onset of spontaneous ventilation in <2 min in three of these four patients. The fourth apneic patient, weighing 117 kg, remained apneic for 6 min after the first dose, and was given a second dose. Spontaneous ventilation began <2 min after the second dose.

In the 18 spontaneously breathing patients, mean rest Pa_{CO_2} decreased slightly after each of three doses of butorphanol. Compared with the baseline Pa_{CO_2} of 57.8 ± 11.1 mm Hg, Pa_{CO_2} levels after the first (55.3, ± 10.9; $P \leq 0.05$), second (52.4 ± 8.38; $P \leq 0.01$), and third (51.7 ± 5.12; $P \leq 0.05$) doses of butorphanol were significantly reduced. The Pa_{CO_2} after the second dose was significantly less ($P \leq 0.05$) than the Pa_{CO_2} after the first dose. Respiratory rate increased significantly from a baseline of 7.8 ± 5.0 min^{-1} to 11.0 ± 4.8 min^{-1} ($P \leq 0.005$) after the first dose of butorphanol. Respiratory rates after the second (12.8 ± 4.4; $P \leq 0.005$) and third (11.9 ± 3.9; $P \leq 0.005$) doses were also significantly above baseline levels, but not statistically different from those observed after the first dose. Tidal volumes increased significantly from a baseline of 469 ± 302 to 844 ± 390 ml ($P \leq 0.005$) after the first dose of butorphanol. Tidal volumes after the second (750 ± 234 ml; $P \leq 0.005$) and third (749 ± 244 ml; $P \leq 0.005$) doses were also significantly above baseline levels, but were not statistically different from those observed after the first dose. Minute ventilation increased significantly from 4.32 ± 2.97 to 8.51 ± 3.14 L/min ($P \leq 0.005$) after the first dose. Minute ventilation after the second (9.20 ± 2.35; $P \leq 0.005$) and after the third (8.63 ± 2.47; $P \leq 0.005$) doses was also significantly above baseline levels, but was not statistically different from minute ventilation after the first dose.

Data on ventilatory response to CO_2 were obtained in eight patients, including three patients who were apneic and intubated on arrival in the recovery room (Figs. 1 and 2). The slope of the baseline CO_2 response curve in the apneic patients was 0, by definition. The slope of the CO_2 response curves increased significantly above baseline levels of 0.36 ± 0.37 to 0.90 ± 0.80 $L{\cdot}min^{-1}{\cdot}mm\ Hg^{-1}$ ($P \leq 0.05$) after the first dose of butorphanol. Slopes after the second (0.99 ± 0.61; $P \leq 0.05$) and third (1.06 ± 0.56; $P \leq 0.005$) doses were also significantly above baseline. The slopes after the second and third dose did not significantly differ from that observed after the first dose of butorphanol. Correlation coefficients for the slope of the baseline and the three butorphanol doses averaged 0.66, 0.84, 0.94, and 0.93, respectively. The correlation coefficient of the baseline slope was poor because data points were erratic because of sighs and periodic breathing.

Surveillance for recurrence of respiratory depression consisted of routine recovery room monitoring. Although the duration of action of butorphanol antagonism of respiratory depression was not formally measured, "renarcotization" did not occur.

Blood pressure and heart rate remained stable after butorphanol, although there was a clinically insignificant increase in systolic blood pressure from a baseline of 143 ± 24.6 to 154 ± 26.5 mm Hg ($P \leq 0.005$) after the first dose of butorphanol, which was maintained after the second and third doses. Epinephrine and norepinephrine concentrations were unchanged after butorphanol.

Pain ranged from none to moderate on arrival in the recovery room and there was no change in the intensity of pain after butorphanol in 16 patients. In two patients pain increased from none to mild, and in three pain decreased from mild to none (one patient) or moderate to mild (two patients). One patient who underwent a shoulder repair awoke after receiv-

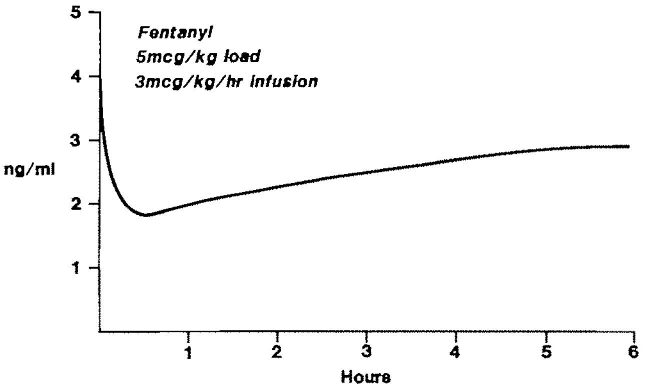

Figure 3. Fentanyl plasma concentrations were simulated with a microcomputer using fentanyl pharmacokinetic parameters determined by McClain and Hug (18,19). After a 5-μg/kg loading dose and a 3-$\mu g \cdot kg^{-1} \cdot hr^{-1}$ infusion, fentanyl concentrations decrease for about 30 min, then increase until steady state is reached (about 15 hr later), or until the infusion is discontinued. The simulation demonstrates that fentanyl concentrations are expected to be increasing during the period of time when ventilatory measurements were made in our study after the administration of butorphanol.

ing butorphanol and immediately complained of severe pain. This patient subsequently required extraordinarily large doses of analgesics, to the point of producing somnolence, without ever obtaining satisfactory pain relief. His blood pressure, heart rate and catecholamine levels were not significantly increased after butorphanol. Psychotomimetic effects, sometimes attributed to agonist-antagonist narcotics, were not noted.

Discussion

Butorphanol improved ventilation and ventilatory responses to CO_2 after fentanyl anesthesia, as evidenced by the onset of spontaneous ventilation in several apneic patients, increased respiratory rate, tidal volume and minute ventilation in spontaneously breathing patients, reduction of resting Pa_{CO_2} levels, and a threefold increase in the slope of the CO_2 response curve. Most of the changes in breathing occurred after the first 1-mg dose of butorphanol. Analgesia was not significantly affected in 21 of 22 patients, and no adverse cardiovascular side effects were observed, although systolic blood pressure increased slightly. Plasma catecholamine concentrations did not increase, suggesting that the adverse effects sometimes seen after the use of naloxone for reversal of narcotics, which have been attributed to increased sympathetic nervous system activity, may not occur with butorphanol.

Plasma levels of fentanyl were not measured in our study. However, the fentanyl infusion was maintained throughout the study, which would result in stable or increasing fentanyl concentrations. The fentanyl concentration expected in a patient with typical pharmacokinetic properties is illustrated in Figure 3 (18,19). Fentanyl concentration increases until a steady state is reached (approximately five half-lives after the start of the infusion, or at about 15 hr). Therefore, the respiratory depression due to fentanyl would tend to increase rather than decrease during the course of the study, leading to an underestimation of the efficacy of butorphanol. End tidal concentrations of isoflurane were very low, $\leq 0.1\%$, at the time the first measurements were made. Of course, this value would tend to decrease with time. However, the fact that most of the improvement in breathing occurred after the first dose of butorphanol, separated by only a few minutes from the baseline measurements, suggests that decreasing end tidal concentrations of isoflurane had little effect on the results. Moreover, low concentrations of isoflurane have been shown not to affect ventilatory response to CO_2 (20).

Rest Pa_{CO_2} did not improve as much as ventilatory responses to CO_2 or minute ventilation after butorphanol. This has been observed previously with naloxone. Naloxone has been given in patients narcotized by morphine in doses such that the CO_2 response improved markedly while rest Pa_{CO_2} was much less affected (21). It appears that rest Pa_{CO_2} levels are determined by a different mechanism than that which determines respiratory "drive", as measured by CO_2 response, and that butorphanol affects drive more than the rest Pa_{CO_2}. That Pa_{CO_2} was reduced to a lesser extent than was the corresponding increase in minute ventilation suggests that either CO_2 production increased substantially after butorphanol, or that the dead space ventilation increased out of proportion to alveolar ventilation. There are no data available at this time to distinguish these possibilities, but the latter would appear most likely.

Further studies will be required to define the clinical usefulness of the ability of butorphanol to antagonize fentanyl. Studies of the effects of butorphanol on the respiratory effects of narcotics other than fentanyl are also needed, as are dose-response studies of butorphanol, nalbuphine, and physostigmine, in which the doses of both the agonist and antagonist are varied. Finally, the antagonist properties of physostigmine, nalbuphine, butorphanol, and naloxone need to be compared in comparable clinical studies. Perhaps after sufficient investigation we will have the knowledge necessary to administer narcotic antagonists effectively without causing postoperative pain or cardiovascular instability.

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Tidal Volumes Required to Maintain Isocapnia at Frequencies from 3 to 30 Hz in the Dog

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KOLTON M, McGHEE I, BRYAN C. Tidal Volumes required to maintain isocapnia at frequencies from 3 to 30 Hz in the dog. Anesth Analg 1987;66:523–8.

We ventilated seven mongrel dogs with high frequency oscillatory ventilation (HFO) at frequencies from 3 to 30 Hz. At each frequency, the tidal volume required to achieve isocapnia ($V_{T_{iso}}$) *was measured by plethysmography. In an individual dog,* $V_{T_{iso}}$ *could be related to frequency by an equation of the form* $V_{T_{iso}} = Kf^{A}$. *A was similar for the seven dogs,* $A = -0.54 \pm 0.03$. *K varied from 179 to 325* $cc - Hz^{-A}$, *reflecting differences between the dogs in dead space,* CO_2 *production and gradient for gas transport. This relation is consistent with that predicted from the data of previous investigators who used different ventilators, circuits and methodology. From 3 to 30 Hz,* $V_{T_{iso}}$ *decreased from 1.2 to 0.4 times anatomic plus equipment dead space, but minute volumes required to maintain isocapnia increased from 6 to 18 times those required during conventional ventilation. We conclude that low tidal volume ventilation is also high minute volume ventilation.*

Key Words: VENTILATION—high frequency.

High frequency oscillatory ventilation (HFO) can support gas exchange over a broad range of frequencies from 3 to 30 Hz (180–1,800 breaths/min) (1). Conventional modeling of gas transport, as summarized by the classical Bohr equation, fails to account for gas flux under these conditions, because at these high frequencies tidal volumes smaller than the sum of anatomic and equipment dead space can maintain normocapnia. To determine just how small these tidal volumes get as frequency increases, we measured the tidal volumes required to achieve steady state isocapnia ($V_{T_{iso}}$) at frequencies from 3 to 30 Hz in the dog. Our findings are compared with those of other studies, and the implications for choice of ventilatory frequency are discussed.

A basic model that can be used to provide a framework for discussion of gas transport during both HFO and CMV is:

$$\dot{V}CO_2 = GRAD \times f \times V_T \times EFF \qquad (1)$$

where $\dot{V}CO_2$ is the rate of CO_2 transport, GRAD is the alveolar-ambient gas concentration gradient, f is the frequency, V_T is the tidal volume, and EFF is an expression for the efficiency of ventilation (2,3). For conventional ventilation $EFF = (1 - V_D/V_T)$, where V_D is the anatomic plus equipment dead space and equation (1) reduces to the classical Bohr equation. During HFO, EFF has the form $a(V_T/V_D)^b f^c$, where a, b, and c are constants. The product $f \times V_T \times EFF$ is referred to as the "effective diffusivity" in some of the HFO literature (2). Previous studies in the normal dog (4–6) have found values for b ranging from 0.5 to 1.2, and a value for c of 0. In terms of Equation 1, we studied the relation between V_T and f, with $\dot{V}CO_2$ equal to the basal CO_2 production of the dog and the determinants of GRAD (arterial and inspired CO_2) fixed during the course of the experiment.

Methods

Anesthesia was induced with sodium pentobarbital (30 mg/kg IV) in seven mongrel dogs ranging in weight from 12.7 to 33.2 kg. Anesthesia paralysis was maintained with intermittent doses of pentobarbital and pancuronium. The dogs were orally intubated with a 9-mm cuffed endotracheal tube. Arterial and venous cannulae were inserted in the femoral vessels and arterial pressure monitored with a Statham P23D

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transducer. Temperature was monitored with a rectal probe. Arterial blood samples were analyzed for pH, Pco$_2$, and Po$_2$ with a Instrumentation Laboratories model 13/03 blood gas analyzer and the values temperature corrected.

The oscillator circuit is diagrammed in Figure 1. The circuit has a T configuration with a Bird 15 mm Jackson Y connector as the center of the T. Sinusoidal flow oscillations were provided by a Metrex Instruments HSMVS oscillator connected to the circuit by a 0.5-m length of 1.2-cm diameter low compliance plastic tubing. A bias flow of fresh gas (10–15 L/m, Fi$_{O_2}$ 0.21) was introduced via standard oxygen delivery tubing to maintain the gradient for gas transport. This flow exited via the low pass filter (LPF), a 2-m length of 0.5-cm diameter Silastic tubing. The proportion of the oscillatory tidal volume delivered to the dog was determined by the relative impedance to the oscillations of the low pass filter and the respiratory system (including the endotracheal tube) of the dog. A screw clamp on the low pass filter allowed the mean airway pressure (MAP) in the circuit to be adjusted. CO$_2$ concentration in the low pass filter (Fe$_{CO_2}$) was measured with a Beckman LB2 analyzer. Airway pressure was measured at the top of the circuit, and the signal passed through two cascaded low pass critically damped filters with a cutoff frequency of 0.05 Hz to derive a mean airway pressure measurement. The value for MAP corresponded within ± 1 cm H$_2$O to measurements of the static intrapulmonary pressure measured when the airway was occluded randomly during the oscillatory cycle (7) and thus reflects the mean distending pressure on the lung during this form of ventilation with this particular circuit (8).

Tidal volumes were measured by placing the dog in a 216-L pressure plethysmograph. The pressure within the plethysmograph was measured with a flush-mounted Validyne MP45, 1–5 cm H$_2$O transducer. Pressure waveforms were recorded on a Beckman Dynagraph Type RM chart recorder. The plethysmograph was statically calibrated and found to be linear over the volume ranges recorded. Volume changes were assumed adiabatic.

The dynamic response of the plethysmograph recorder system was determined by introducing a sinusoidal flow signal of fixed volume amplitude into the plethysmograph at various frequencies over the range 3–30 Hz. At each frequency the tidal volume as measured by the plethysmograph (output) was expressed as a fraction of the output in response to a signal of the same input amplitude at 3 Hz. A dynamic calibration curve was produced by plotting this ratio vs frequency; this was repeated for several tidal volumes. The curve was flat up to 15 Hz and then it linearly increased to a maximal overshoot of 20% at 30 Hz; the tidal volumes recorded during our experiment were corrected on the basis of this curve. Critical to our method of calibration was the constancy of the input volume signal to the plethysmograph over this frequency range. The input signal was generated by the oscillator (a diaphragm pump with low compressible volume) that was attached directly to the plethysmograph to avoid Helmholtz resonance effects (9). We confirmed that the oscillator was a constant tidal volume source over this range of frequencies by measuring its output with a high fidelity plethysmograph-recorder system. This consisted of a 2.5-L glass bottle in which pressure was measured with a Millar micromanometer pressure transducer and the signal recorded on a Gould ES1000 electrostatic recorder. At a fixed stroke displacement, the oscillator's output, as measured by the amplitude of the pressure swings in the bottle, remained constant as the frequency was varied between 3 and 30 Hz.

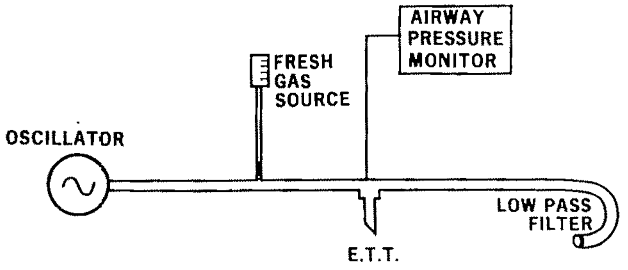

Figure 1. High frequency oscillation circuit.

Each dog was initially ventilated to a selected Paco$_2$ with a Bennett MAI ventilator at conventional rates and tidal volumes, Fi$_{O_2}$ 0.21. Expired gas was collected for measurement of minute ventilation and mixed expired CO$_2$, and these values were used to calculate the CO$_2$ production.

The dog was then placed in the plethysmograph and oscillated at frequencies from 3 to 30 Hz. At each frequency the tidal volume was adjusted (guided by the Fe$_{CO_2}$ × FGF product) to achieve a CO$_2$ flux equal to the basal CO$_2$ production. After 10 min of oscillation, arterial blood was analyzed and, if isocapnia had been maintained, tidal volume was measured. The number of different frequencies studied in each dog over an 8-h period varied from 13 to 23. With each measurement of Vt$_{iso}$ the MAP, Paco$_2$ and Fe$_{CO_2}$ were recorded. The frequency range was scanned four times to minimize the impact of time-related changes in the study parameters (chiefly the basal CO$_2$ production of the dog) occurring during the course of the day. Paco$_2$, bias flow, and mean airway pressure were maintained constant in any one dog.

Table 1. Summary of Data

Dog	Weight (kg)	VD (cc)	Pa_{CO_2} (mm Hg)	FE_{CO_2}	$\dot{V}CO_2$ (ml/min)	MAP (cm H_2O)	A	K	r^2	n
1	33.2	157	44 ± 1	1.36 ± 0.04	200 ± 18	8.7 ± 1.7	−0.52	325	0.93	23
2	22.7	115	39 ± 2	1.32 ± 0.07	131 ± 7	8.3 ± 0.6	−0.50	252	0.95	18
3	21.4	110	44 ± 2	1.34 ± 0.08	135 ± 8	6.9 ± 0.7	−0.53	240	0.96	20
4	22.4	114	40 ± 2	1.07 ± 0.03	107 ± 3	7 ± 0.3	−0.58	257	0.90	13
5	15.4	86	30 ± 2	0.83 ± 0.06	84 ± 6	7.4 ± 0.6	−0.52	200	0.88	23
6	16	88	35 ± 2	1 ± 0.06	101 ± 6	8 ± 0.3	−0.55	221	0.90	21
7	12.7	75	37 ± 3	0.86 ± 0.07	88 ± 7	7.1 ± 0.2	−0.58	179	0.97	14
Mean	20.5	106	38.4	1.1	121	7.6	−0.54	239	0.93	19

Results

All animals tolerated the HFO well; oxygenation, cardiovascular stability, and isocapnia were maintained at all frequencies. Table 1 summarizes the means and standard deviations for each dog over the course of the experiment for the variables Pa_{CO_2}, FE_{CO_2}, $\dot{V}CO_2$ and MAP. $\dot{V}CO_2$ was calculated from FE_{CO_2} multiplied by the fresh gas flow. VD is calculated as the sum of anatomic dead space (estimated as 4 ml/kg of body weight) plus the volume of the endotracheal tube (13 cc).

For each dog VT_{iso} was plotted as a function of frequency. The plots suggested a relation of the form $VT_{iso} = Kf^A$, and the data were fitted to this curve by performing a linear regression on the logarithmic transformations of the variables f and VT_{iso}. The values for the exponent A in the seven dogs ranged from −0.5 to −0.58, with a mean −0.54 ± 0.03. K varied from 178 to 326 cm-Hz^{-A}, and R^2 for the fitted curves from 0.88 to 0.97. Examination of residuals confirmed that the curves were a good fit to the data over the entire range of frequencies. Plots of the regression curves for the seven dogs appear in Figure 2.

K varied widely between dogs, reflecting the differences in $\dot{V}CO_2$, GRAD, and VD in the animals. The exponent b in the expression for EFF of equation (1) is related to A by $b = -(1 + 1/A)$. With a value for A of −0.5, $b = 1$, and thus (1) predicts K should be proportional to $\sqrt{\dot{V}CO_2 \times VD / Grad}$. R^2 for a regression of K on the corresponding value for $\sqrt{\dot{V}CO_2 \times VD / Grad}$ (calculated using the mean values for these parameters over the course of the experiment) was 0.92.

The data for the entire group of seven dogs were combined for analysis of CO_2 transport efficiency during HFO. Efficiency was defined as the ratio of alveolar ventilation to minute ventilation (2,10). Alveolar ventilation was calculated as $\dot{V}CO_2$ / GRAD, where GRAD was estimated by the arterial minus the low pass filter CO_2 gradient instead of the more conventional alveolar to inspired gradient. Efficiency was calculated for each of the VT_{iso} measurements made in these experiments using the values for Pa_{CO_2}, FE_{CO_2}, and FGF collected at the same time. Efficiency is graphed as a function of frequency in Figure 3.

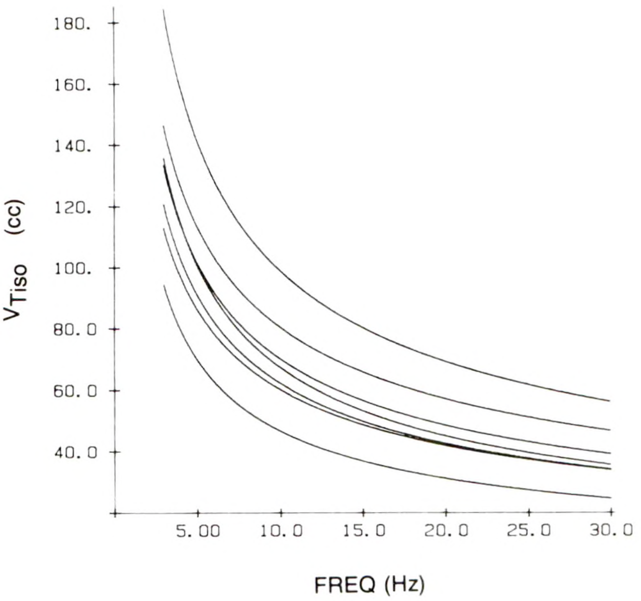

Figure 2. Regression lines relating tidal volumes required for isocapnia (VT_{iso}) to frequency for the seven dogs.

Discussion

In this series of dogs we have studied CO_2 transport during HFO by measuring the tidal volumes required to induce a constant gas flux (basal CO_2 production) at frequencies in the range 3–30 Hz. In an individual dog, the major parameters other than tidal volume and frequency that might affect gas transport were kept constant; these included the lung volume (MAP) and gradient across which gas was transported.

Critical to the results is the accuracy of our method

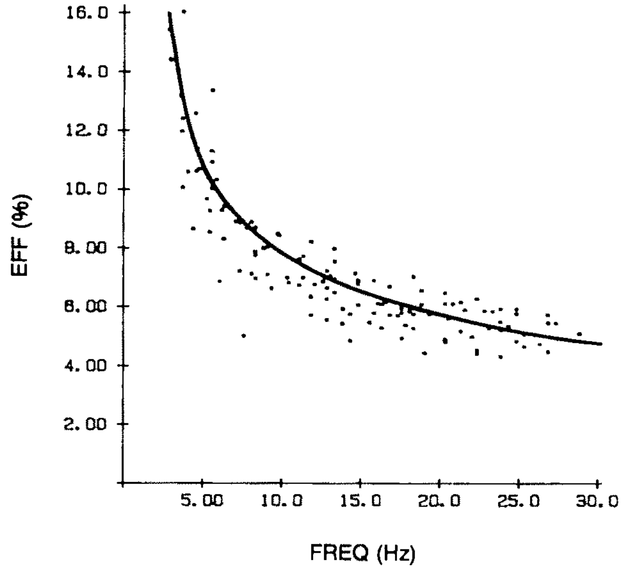

Figure 3. Efficiency (alveolar ventilation as a percent of minute ventilation) vs frequency for the 132 observations in this experiment.

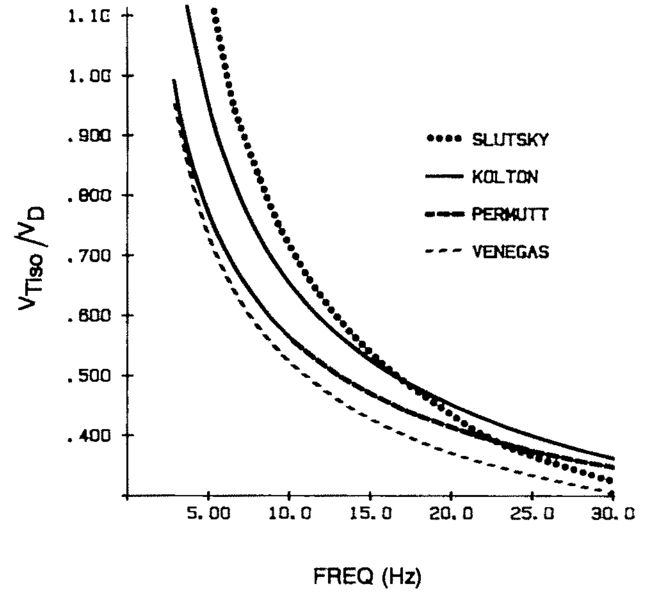

Figure 4. Predicted $\mathrm{V_T/V_D}$ vs frequency relation from the data of Slutsky (4), Weinmann (6), Venegas (5) (dashed line = extrapolated portion of curve), and those found in our experiment.

for measuring VT_{iso}. Measurement of tidal volume over this broad range of frequencies presents several problems. The open configuration of the circuit and resonance effects (9) preclude the substitution of ventilator stroke volume for the volume delivered to the dog. At the high frequencies, large flow rates, and small tidal volumes generated by HFO, conventional pneumotachometers represent a significant impedance and equipment dead space, and may have calibration curves that are alinear and frequency dependent (11). Tidal volumes were therefore measured using a pressure plethysmograph that had been statically and dynamically calibrated.

In each dog VT_{iso} decreased monotonically with increases in frequency from approximately 1.2 times the calculated anatomic plus equipment dead space at 3 Hz to one-third of that volume at 30 Hz. The data could be fitted to a curve of the form $\mathrm{VT}_{iso} = Kf^A$ with a mean value for A in the seven dogs of -0.54. K varied widely between dogs reflecting the differences in basal CO_2 production, gradient, and anatomic dead space of the seven dogs. Because A is less than 1, VT_{iso} does not decrease proportionately as frequency increases, and thus the minute ventilation required to maintain isocapnia, $\dot{V}_{iso}$, increases with frequency; $\dot{V}_{iso} = Kf^{0.46}$. To halve VT_{iso}, one must approximately double the minute volume of ventilation.

A measure of gas transport efficiency is the ratio of alveolar ventilation (CO_2 flux normalized for gradient) to minute ventilation. In Figure 3 the efficiency calculated for each observation in the seven dogs is plotted vs frequency. Efficiency decreases from 15% at 3 Hz to 5% at 30 Hz; this compares with an efficiency of 60–70% at the tidal volumes and frequencies used for conventional mechanical ventilation. Minute volumes at 3, 15, and 30 Hz were approximately 6, 12, and 18 times those required to maintain isocapnia with conventional ventilation. Other studies (4,5) have shown that in the normal dog gas flux is linearly proportional to frequency (making efficiency independent of frequency). This suggests that the decrease in gas transport efficiency in Figure 3 is a consequence of the smaller tidal volumes associated with isocapnia as frequency increases (Fig. 2). Several explanations have been proposed for this "tidal volume effect," but central to them is the concept that as tidal volume decreases the contribution of bulk flow to total gas transport decreases, making transport increasingly dependent on relatively inefficient (in terms of minute volumes) mixing processes (12–14). High frequency, small tidal volume ventilation is also high minute volume ventilation.

It is possible that the VT_{iso} – frequency relations we found are predominantly a reflection of our particular ventilator, circuit, or method for measuring tidal volume. For this reason our data are compared with those of three other studies that used quite different ventilators, circuits, fresh gas flow rates, and methodology. Slutsky et al. (4) measured the rate of CO_2 transport induced by short (< 30 sec) bursts of

HFO at various frequency tidal volume combinations. Venegas et al. (5) used the washout of nitrogen-13 to estimate the alveolar ventilation as a function of frequency and tidal volume. Weinmann et al. (6) measured VT_{iso} by plethysmography but over a lower frequency range from 0.25 to 8 Hz. The regression equations describing the data in two of these experiments are in the form of Equation 1; EFF in the Venagas study was $0.15 \times (VT/VD)$; and in the Weinmann study $0.19 \times (VT/VD)^{1.2}$. The regression equation in Slutsky's study has the form $\dot{V}CO_2 = 0.0003\ f^{1.1} \times VT^{1.5}$. These three equations were used to predict VT_{iso} as a function of frequency for a dog with $\dot{V}_{CO_2}$ 125 ml/min and VD 100 ml (the mean values for these variables in this study and also those of Weinmann and Slutsky). The value for GRAD was 0.05 in the studies of both Slutsky and Venegas and 0.037 in our study and that of Weinmann. In Figure 4, we have plotted the regression curve relating VT/VD to frequency for our 132 data points ($VT/VD = 2.3 \times f^{-0.55}$, $r^2 = 0.90$) along with the curves predicted by the above equations. The curves from all four studies are similar in shape despite the diversity in methodology and ventilators among the studies. They predict that normocapnia can be achieved with tidal volumes smaller than dead space and that CO_2 transport efficiency decreases with increases in frequency. VT_{iso} levels in Permutt's experiment were only measured for frequencies from 0.25 to 8 Hz but the curve is extrapolated to 30 Hz (dashed line in Fig. 4) based on their quantitative model (3) using a value for the coefficient of dispersion suggested by their low frequency data (6). Their model predicts VT_{iso} remarkably well over the broad range from 0.25 to 30 Hz.

Tidal volume cannot be the sole criterion in choosing ventilatory frequency. The decrease in VT_{iso} as frequency increases from 3 to 30 Hz is accompanied by a threefold increase in $\dot{V}_{iso}$, from six to 18 times that required with conventional ventilation. The effects of these high flows on intrapulmonary pressures, mucociliary clearance, distribution of ventilation and potential for gas trapping may limit or suggest optima for ventilatory frequency.

For example, both airway pressure amplitude and dynamic hyperinflation are strongly dependent on the minute volume of ventilation. Airway pressure amplitude is a function of flow amplitude and respiratory system impedance (15,16), and it will depend on the sum of the elastic, viscous, and inertial forces that must be overcome in moving gas into and out of the lung. As frequency increases VT_{iso} decreases, and thus the pressure required to overcome elastic forces decreases; but, at the same time, flow velocity and acceleration increase, making viscous and inertial pressure losses greater. As a result, the airway pressures generated at isocapnia are not necessarily a monotonic function of frequency, and at the higher frequencies may exceed those found with conventional ventilation (17). With regard to dynamic hyperinflation, there may be limits to the minute volumes that can be supported by the respiratory system without regional or global gas trapping occurring (18,19). Dynamic hyperinflation during HFO has been demonstrated by some investigators (7,18) but not others (8), and it has been suggested that factors other than minute ventilation, such as the circuit design, ventilatory waveform, lung volume, and respiratory system compliance are also important in determining whether it occurs. Nevertheless the large increase in $\dot{V}_{iso}$ with frequency must remain a concern in this regard.

In summary, in the normal dog, using a particular ventilator and circuit combination, we have found that tidal volume required to achieve steady state isocapnia decreases monotonically as frequency increases. The decreases in tidal volume are accompanied by increases in minute ventilation that may place upper limits on the frequencies that can be used during this form of ventilation. Our findings are consistent with those of other investigators who have used different methods, ventilators, and circuits to study gas exchange. Because gas transport during HFO may be more sensitive to the mechanical properties of the lung than during conventional ventilation the relations we found may not be applicable to other species or in pathologic states (19–22).

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Removal of Tracheal Secretions in Anesthetized Dogs:

Balloon Catheters versus Suction

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LEIMAN BC, KATZ J, STANLEY TH, BUTLER BD. Removal of tracheal secretions in anesthetized dogs: balloon catheters versus suction. Anesth Analg 1987;66: 529–32.

Artificial secretions were removed by suction (using 12- or 18-French suction catheters) or by means of a balloon-tipped catheter (6-French Fogarty® arterial embolectomy catheter) in 20 experiments performed on five dogs anesthetized with halothane. Each dog had 5 ml of mucin injected 10 cm down the endotracheal tube prior to a 30-sec period of intermittent positive pressure ventilation. After this procedure, the ventilator was disconnected and the secretions were removed by suction with the 12- or 18-French catheters or by the Fogarty catheter. Each dog had balloon removal performed twice and suction performed once with the 12-French and once with the 18-French catheter. The endotracheal tube was cleaned and a 15-min stabilization period was allowed between each experiment. Arterial blood pressure (MAP) and pulmonary artery pressure (PAP) did not change after either technique. There were no ECG changes, arrhythmias, or alterations in Pa_{CO_2}. *The* Pa_{O_2} *was significantly lower in the two suction catheter groups [520 ± 33 mm Hg (12 French) and 451 ± 31 mm Hg (18 French)] than in the balloon removal group (564 ± 10 mm Hg)* ($P < 0.05$). *The balloon technique removed more secretions (4.52 ± 0.06 ml) than did suction (12 French, 1.32 ± 0.17 ml; 18 French, 2.11 ± 0.44 ml). Balloon removal of tracheal secretions has two advantages over conventional suction techniques: it removes more secretions, and it has less detrimental effect on arterial oxygenation.*

Key Words: LUNG—secretions.

Tracheal secretions are usually removed by passing a suction catheter down the endotracheal tube. This procedure may be ineffective, especially when secretions are viscid (1). In spite of meticulous technique, suctioning may be associated with complications including mucosal damage, hemorrhage, and erosion (2). Furthermore, hypoxemia can also occur during endotracheal suctioning and has been implicated in occasional deaths (3). The amount of secretions removed by suctioning varies depending upon the adequacy of technique and the fluidity of the secretions. Viscous secretions may be strongly adherent to the walls of the airways and difficult to remove.

Secretions may also be removed using a balloon-tipped Fogarty® arterial embolectomy catheter (4). With this technique the balloon is passed beyond the secretions in a deflated state, inflated and then slowly withdrawn. Secretions are passively pulled up by this maneuver and thus removed from the trachea and the endotracheal tube. The object of this study was to compare the effectiveness of balloon catheters and suction as methods for removing experimentally produced tracheal secretions in anesthetized dogs. In addition, the influence of both techniques on Pa_{O_2}, Pa_{CO_2}, heart rate, arterial blood pressure, and the incidence of arrhythmias was also evaluted.

Methods

Twenty experiments were conducted on five mongrel dogs weighing 18–23 kg. The experiments were of three types. In the first type (conducted twice in each animal), secretions were removed with a Fogarty arterial embolectomy catheter; in the other two types (conducted once in each animal), secretions were aspirated with a 12- or an 18-French suction catheter (Bard). Anesthesia was induced with IV thiopental, 25 mg/kg, followed by tracheal intubation with a 9.0-mm diameter, 30-cm long cuffed endotracheal tube (Portex). Mechanical ventilation was initiated with a positive pressure ventilator (Harvard) and anesthesia maintained with halothane (0.8–1% inspired) in ox-

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Table 1. Arterial Oxygen Tensions

Suction PO_2 (mm Hg)			Balloon PO_2 (mm Hg)	
Baseline	12 French	18 French	Baseline	Balloon
599 ± 10 (n = 10)	520 ± 33[b] (n = 5)	451 ± 31[b] (n = 5)	589 ± 11 (n = 10)	564 ± 10[a] (n = 10)

Values are mean ± SEM.

[a] Denotes significant difference ($P < 0.05$) between suction (12 and 18 French) and balloon.

[b] Denotes significant difference ($P < 0.05$) between baseline and suction.

ygen. An arterial catheter was inserted in the left femoral artery to continuously monitor blood pressure (MAP) and another catheter inserted in the abdominal aorta via the right femoral artery to obtain blood samples for blood gas analysis (Instrumentation Laboratories 1303). Pulmonary artery and left ventricular catheters were placed to measure pulmonary artery pressure (PAP) and left ventricular end-diastolic pressure (LVEDP). Heart rate and rhythm were continuously recorded from lead II of the ECG. The PaO_2 was maintained between 35 and 40 mm Hg by adjusting tidal volume and rate of the ventilator.

After a 30-min stabilization period, baseline data were collected and an arterial blood sample for gas analysis obtained. The ventilator was then momentarily disconnected and 5 ml of mucin (commercial mucin powder, Sigma) mixed in a ratio of 1 g mucin to 0.4 ml water was injected through a catheter inserted 10 cm into the endotracheal tube. After 30 sec of continued positive pressure ventilation, the ventilator was again disconnected from the endotracheal tube and the mucin removed using either a Fogarty catheter or suction. The former consisted of passing a 6-French Fogarty arterial embolectomy catheter 35 cm down the endotracheal tube, inflating the balloon with 2 ml of air and withdrawing the catheter over 15 sec. The secretions extracted on the proximal side of the balloon were collected into preweighed vials. Suctioning was performed by passing a 12-French or an 18-French catheter (Bard) 35 cm down the endotracheal tube and then applying suction while withdrawing the catheter over 15 sec. The suction apparatus was set to maintain a displacement of approximately 25 L/min and to generate a negative pressure of 250 mm Hg. The volume of secretions removed was determined by weighing.

Arterial blood samples were obtained for blood gas analysis before the injection of mucin (baseline) and immediately after removal of the Fogarty catheter or completion of suctioning before reconnection of the ventilator. Blood pressure and heart rate were recorded continuously during this period (Gould 2600) and the incidence of arrhythmias noted. The endotracheal tube was cleaned and a stabilization period of 15 min was allowed before the experiment was repeated.

Statistics

Data were analyzed using a two-way analysis of variance; $P < 0.05$ was regarded as statistically significant.

Results

There were no significant changes in heart rate, blood pressure, or pulmonary artery pressure with either of the two suction techniques or with balloon extraction. No arrhythmias were recorded. The animals made no effort to breathe spontaneously during the extraction of mucin. Table 1 shows the PaO_2 levels after suction with the 12- and 18-French catheters and with the balloon-tipped catheter. The PaO_2 was significantly lower in the two suction groups [520 ± 33 mm Hg (12 French) and 451 ± 31 mm Hg (18 French)] than in the balloon group (564 ± 10 mm Hg) ($P < 0.05$). The decrease in PaO_2 in the suction groups was also significantly below the baseline levels (599 ± 10 mm Hg). Balloon removal did not significantly decrease PaO_2 below baseline levels (589 ± 11 to 564 ± 10 mm Hg). There was no change in $PaCO_2$ in any of the groups.

Table 2 shows the volume of artificial secretions recovered by the two different methods. The balloon technique recovered 4.52 ± 0.06 ml of the 5 ml of mucin injected compared to the recovery of 1.32 ± 0.17 ml with the 12-French suction catheter and 2.11 ± 0.44 ml with the 18-French suction catheter. The difference between balloon removal and both suction catheter groups was significant ($P < 0.05$), whereas there was no statistical difference in the volume of secretions removed by 12-French and 18-French suction catheters.

Discussion

Insertion of an endotracheal tube often stimulates secretions that require mobilization and/or removal.

Table 2. Recovery of Artificial Endotracheal Secretions

Suction (ml)		Balloon (ml)
12 French	18 French	12 French
1.32 ± 0.17 (26%) (n = 5)	2.11 ± 0.44 (42%) (n = 5)	4.52 ± 0.06* (90%) (n = 10)

Values are mean ± *SEM*. Numbers in brackets are percentage recovered.
*Denotes significant difference ($P < 0.05$) between suction (12 and 18 French) and balloon.

Traditionally, this has been accomplished by suction, a method associated with complications of which hypoxemia is the most serious (5). The effects of hypoxemia may be reflected by disturbances in cardiac rhythm (6) and are more pronounced in the critically ill patient (7). Hypoxemia during tracheal suctioning is caused by oxygen enriched air being replaced with entrained ambient air while varying degrees of negative pressure are applied to the lungs (8). The degree of hypoxemia depends upon the size of the catheter and the ratio between the outer diameter of the catheter and the inner diameter of the endotracheal tube (8). These effects are more pronounced with prolonged suction, a low F_{IO_2}, or impaction of the suction catheter in a small airway, and they can even occur in patients with no known pulmonary disease (9). The greater decrease in PaO_2 after aspiration with the 18-French catheter and with the 12-French catheter reflects the fact that greater negative pressure was applied to the airways. With the use of the Fogarty balloon the only negative pressure is that resulting from extracting the volume of gas above the inflated balloon. The dogs in this experiment had no cardiopulmonary disease and were breathing 100% oxygen. Consequently, acute hypoxemia and hypoxia-induced cardiac arrhythmias did not occur in spite of large decreases in PaO_2 after suction. Vagal stimulation secondary to tracheal irritation may also cause cardiac arrhythmias (10) but the absence of arrhythmias in the present study indicates that the animals remained adequately anesthetized and oxygenated. Although the difference in oxygen tensions before and after suctioning resulted in little change in oxygen content in the dogs in these experiments, similar decreases in PaO_2 after suction in patients with pulmonary disease can, and have been shown to, result in significant hypoxemia (7). We believe the Fogarty catheter technique may be of greatest benefit in critically ill patients.

The aim of suctioning or of the use of a Fogarty catheter is to remove secretions. In this respect, the Fogarty catheter was significantly better than suctioning (Table 2). Although more secretions were removed with 18-French than with 12-French catheters, the difference was not statistically significant and any possible advantage of the larger catheter was achieved at the expense of a greater decrease in PaO_2. The more viscid the secretions the more likely they will adhere to the walls of the tracheobronchial tree and endotracheal tube. In this situation a suction catheter wil preferentially suction a gas rather than a liquid. In contrast, a balloon-tipped catheter will more easily remove the secretions in its path.

Another disadvantage of suctioning is the potentia for mucosal damage (1,2). While applying suction, stripping of the mucosa may occur upon withdrawa of the catheter (1). Also, transient bacteremia, which may occur after tracheal suctioning in ventilated neonates, is considered to be a source of septicemia and results from mechanical trauma to the tracheal mucosa, which is then colonized with opportunistic organisms very early after intubation (11). In this study no attempt was made to examine the airways for mucosal damage, although it seems unlikely that a soft-tipped balloon catheter possesses much potential for producing mucosal damage.

During endotracheal tube suctioning, three potentially undesirable effects occur that may increase intracranial pressure and may result in neurologic deterioration (12). They include: 1) a period of apnea leading to hypoxemia; 2) variations in intrathoracic pressure during hyperventilation and apnea; and 3) stimulation of the trachea. The increase in ICP during suctioning has been attributed more to the stimulation of the trachea, than to an increase in $PaCO_2$ during apnea (13). Balloon removal of secretions, on the other hand, causes less hypoxemia, does not require prior hyperventilation, and appears to be less traumatic to the tracheobronchial mucosa and may, therefore, minimize increases in ICP.

In conclusion, we have demonstrated that remova of artificial tracheal secretions can be accomplished with less effect on PaO_2 by use of a Fogarty catheter than by use of suction, and that significantly more of the secretions are removed. Use of Fogarty catheters deserves clinical study where its beneficial effects can be more fully evaluated.

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Lack of Effects of Prenatal Exposure to Lidocaine on Development of Behavior in Rats

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The objective of this investigation was to study the effects of lidocaine upon postnatal development of the rat. Lidocaine, 6 mg/kg (21 μmol/kg), was given to a group of 12 rats. Injections were administered intramuscularly, bilaterally in the masseter muscles, once a day on days 10 and 11 of pregnancy. Twelve control rats were given physiologic saline. Clinical signs, mortality, body weight, and food consumption were recorded during pregnancy and lactation. The duration of gestation was also recorded. The development of the offspring was monitored by tests of spontaneous activity, nociception, learning ability, and physical development. No clinical signs of adverse reactions were seen in any of the groups. In the majority of the learning ability tests, the control and lidocaine-treated groups showed similar results. However, in the schedule of differential reinforcement of low rates of responding (DRL 20), the lidocaine-exposed males received more reinforcements than the controls and made fewer resposes. In the tests of nociception, a significant difference between sexes was recorded, in that the females were more sensitive than the males in the shock-titration test. Physical development, as monitored by swimming ability and spontaneous activity, showed no intergroup difference. The present results indicate that prenatal exposure to lidocaine fails to result in postnatal impairment of the development of behavioral performance of a wide range of tasks.

Key Words: ANESTHETICS, LOCAL—lidocaine.

Prenatal administration of neuroactive compounds may produce alterations in the behavior of the offspring. Some investigators have reported behavioral changes in the offspring of pregnant animals exposed to halothane (1,2).

A study of neonatal visual preference patterns (3) indicated a significant difference between a group of human infants exposed prenatally to anesthetics and their control group. The infant group prenatally exposed to local anesthetics attended more to individual objects and shifted attention less from object to object. It was suggested that prenatal exposure to local anesthetic compounds may alter the later development of perceptual and/or cognitive function. In a study in rats (4), the offspring of female rats treated with a single dose of local anesthetic compounds showed a decreased performance in some developmental tests, in the performance of an instrumental learning task (light/dark discrimination), and in an increased leve of motor activity. However, in this study the result were not conclusive because the group sizes wer very small.

The objective of this investigation was to study th effects of lidocaine upon pregnancy and postnatal development of the rat, with emphasis on the effects o maturation and development of the offspring.

The test compound, lidocaine, is an anesthetic tha is most often used in infiltration anesthesia. Rats wer used because this species historically has been use in this type of study. Moreover, our laboratory possesses background data on the particular strain used The lidocaine was injected intramuscularly, in th masseter muscles. This route of administration an the dose were chosen with an awareness to its clinica usage in dental practice. As a double safeguard, double injections were used (days 10 and 11 of pregnancy), whereas a previous investigation (4) used onl a single injection (day 11).

The behavioral tests performed in this study wer selected as standard for the monitoring of physica development, learning ability in both positively an negatively reinforced tasks, and nociception.

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Materials and Methods

Animals

Twenty-four female Sprague-Dawley rats (weighing 245–295 g, aged 110–130 days, from Alab AB, Sollentuna, Sweden) were used in the experiment. They were housed in laboratory conditions with a 12-hr light/dark schedule in a room thermostatically maintained at 21 ± 1°C, with a relative humidity of 40–80%. These rats were mated after acclimatization to laboratory conditions. The subjects were the litters, both sexes, of these rats.

Experimental Design

Two groups of 12 mated female rats were given either lidocaine or physiologic saline on days 10 and 11 of pregnancy. The rats were allowed to litter, and the litters were normalized to four pups of each sex on day 3. Standard clinical surveillance was conducted during pregnancy, delivery, and lactation (see below). At weaning (day 25), ten litters from each group were selected for further study. Subgroups were created, each consisting of one male and one female from each litter. The subgroups were selected for developmental tests so that subgroup 1 was used for activity measurements and tests of nociception, subgroup 2 for conditioned avoidance responding (CAR) tests, subgroup 3 for light/dark discrimination (L/D) tests and differential reinforcement of low rates of responding (DRL), and subgroup 4 was kept as a reserve. All behavioral tests were performed when the offspring were 60–80 days old. A cross-fostering procedure was not applied because the object of the investigation was 1) to produce conditions that would increase the probability of any behavioral teratologic effects by using a double injection procedure and increasing the number of animals per group, and 2) to test whether the alterations obtained previously (4) could be reproduced (no cross-fostering was used in that study). All behavioral tests were performed blind, that is, the experimentor was not aware of the prenatal treatment of the animals.

Mating Procedure

During the mating period, five females and two males were housed together and allowed to mate overnight. The day of occurrence of vaginal plug and/or sperm in the vaginal smear was considered day 0 of pregnancy. Each day, the mated females were divided evenly between control and test groups. Mated females were housed individually.

Dosing

Lidocaine hydrochloride (Batch no.105, Astra Läkemedel AB, Sweden) was dissolved in physiologic saline to a concentration of 7.5 mg/ml; 0.8 ml/kg body weight was injected intramuscularly, bilaterally in the masseter muscles, once a day on days 10 and 11 of pregnancy. Control animals received 0.8 ml/kg of saline.

Clinical Observations of the Pregnant Rats

All animals were clinically evaluated. Body weights were recorded on day 0 and then every third day during gestation and on days 1, 3, 7, 14, and 21 after delivery; mean body weight was calculated for each group. Food consumption was determined weekly except on the days when injections were given, when it was measured daily. Food consumption was calculated as the difference between the food offered and the amount remaining in the feeders, the mean daily food consumption calculated for each group. Water consumption was assessed daily by visual inspection of the water bottles.

Gestation period. The day of delivery, day 0 postparturition, is defined as the day vaginal bleeding is observed or the day delivery of the first pup. The definition is valid if delivery is completed on the following morning.

Clinical Observations of the Litters

The litters were examined after delivery for litter size, number of living pups, and gross abnormalities. Keeping nest disturbance to a minimum, we inspected all litters daily. Litter weights (viable pups) and the number of pups in each litter were recorded at delivery and again on days 7 and 21.

On day 3, the litters were normalized to four pups of each sex. Some litters contained an insufficient number of pups and were therefore complemented with pups from another litter within the same group. The times of physical developmental milestones, such as pinna unfolding, tooth eruption, and eye opening were recorded.

Behavioral Studies of Offspring

Negative geotaxis. Negative geotaxis was tested on 5 consecutive days, from day 5. All pups were tested in this trial, that is, all members of all litters. The pups were placed on a board at a 30° angle to the horizontal plane with their heads downward. The time required for the pup to complete a full 180° turn was recorded.

Activity. Locomotion, rearing, and total activity were measured over 30-min periods using Motron Mark 24 Fc/R instruments, automated devices that utilize photocell beams to register activity counts (5). Two experiments were performed: 1) male and female control and lidocaine groups were tested at 60 days of age, and 2) male control and lidocaine rats were tested at 90 days of age.

Conditioned avoidance responding (CAR). The two-way active avoidance procedure was performed as previously outlined (6).

A shuttle box apparatus consisting of two identical compartments with a grid floor was used. Scrambled foot shock was delivered through the grid floor (shock generators, model 521/C, and scramblers, model 521/S, Campden Instruments Ltd., England). Crossings from one compartment to the other were detected by four photocells (model E35-DS200, Omron Tateisi Electronics Co., Japan), and relayed to a PDP11/04 computer (Digital Equipment Corporation, United States). Droppings were collected in a metal tray placed beneath the grid floor, and the shuttle boxes were housed in soundproof plywood chambers with windows to allow continuous observation of the rats.

Avoidance and escape responses, failure to respond, and response latencies for each trial were recorded. The number of intertrial crossings made during the start-up and the number of intertrial crossings (ITCs) were also recorded. The avoidance response was defined as crossing to the other compartment when subjected to a conditioned stimulus (CS). The CS was a 10-sec tone signal (1000 Hz). The escape response was defined as crossing to the other compartment when subjected to an unconditioned stimulus (US), which followed the CS if no avoidance response had been made. The US was a 5-sec scrambled shock (1.0 mA). Failure to respond was defined as absence of any crossing upon the termination of CS–US (15 sec). The two-way active avoidance (CAR) acquisition training consisted of five sessions of 20 trials on each of 5 consecutive days. At the start of the first or the single session, each rat was placed in one compartment of the shuttle box and allowed a 10-min period of free exploration prior to the first trial (start-up time). The intertrial interval was constant at 40 secs.

Tests of nociception Shock-titration testing was carried out in a specially constructed test box (25 × 26 × 30 cm, Campden Instruments Ltd.), wired to present scrambled foot shock, and balanced upon four strain gauges (one at each of the four corners) so that a rat's movements was recorded (7,8). Shocks (0.75 sec) were delivered to the grid floor of the test box by a shock generator and shock scrambler (models 521/E and 521/S, Campden Instruments Ltd.). Titrations were continued upward or downward, depending on nonresponse or response at the 50-, 75-, 100-, 125-, 150-, 175-, 200-, 250-, and 300-μA intensities in a stepwise, incremental manner, after a 3-min habituation to the box.

Table 1. Negative Geotaxis after Prenatal Lidocaine Exposure

	Latency (sec)			
Day number	Control males (48)	Lidocaine males (48)	Control females (48)	Lidocaine females (48)
5	16.9 ± 1.5	18.6 ± 1.7	17.9 ± 1.2	17.1 ± 1.7
6	15.3 ± 1.3	15.2 ± 1.2	13.0 ± 1.1	14.1 ± 1.1
7	11.4 ± 0.7	11.0 ± 0.9	10.7 ± 0.7	10.4 ± 0.7
8	10.8 ± 0.9	11.2 ± 1.0	11.6 ± 0.8	11.3 ± 1.5
9	9.4 ± 0.6	8.8 ± 0.8	10.7 ± 0.6	9.4 ± 0.7
10	9.4 ± 0.7	7.5 ± 0.9	8.8 ± 0.6	8.6 ± 1.0

Male and female pups were tested at 5–10 days of age.
Values are expressed as group mean ± SEM.
No significant effects of the treatment were obtained.

Hot-plate testing was conducted with an analgesia meter (model 35, IITC Inc., United States) as described elsewhere (9). The animals were adapted to the test procedure by a prior exposure to the test apparatus. During testing, the rats were confined to the hot plate set at 58 ± 2°C, by a Plexiglas chamber (27 × 28 × 26 cm). Time to onset of licking of the paws or the vigorous shaking of a paw was recorded.

The tail-flick test was conducted with an analgesia meter (model 33, IITC Inc.), as described previously (10). The rats were adapted to the restraining tube on each of three consecutive daily 10-min sessions on the 3 days before testing. During testing a rheostat-controlled light beam was focused on the tip of the tail and the time from the onset of the heat stimulus to the flick of the tail was recorded on two occasions (tail-flick latency).

Light/dark discrimination. Rat test cages (model No.410, Campden Instruments Ltd.) were used. The animals (total number of animals was 36, with nine animals per group) were deprived of food to 80% of their free-feeding weights and shaped to bar press, the reinforcer being a liquid diet consisting of egg, sugar, 0.9% saline, and tap water (1:50 g:50 ml:50 ml). The animals were weighed both before and after sessions and the standard diet was provided after ses-

Table 2. Spontaneous Motor Activity after Prenatal Lidocaine Exposure

	Control males	Lidocaine males	Control females	Lidocaine females
First experiment:				
Locomotion	47 ± 8	45.5 ± 11	50.5 ± 9	42.5 ± 3
Rearing	223.5 ± 55	253 ± 60	325 ± 62	286 ± 47
Motility	3094 ± 270	3179 ± 607	2918 ± 526	2708 ± 159
Second experiment:				
Locomotion	42 ± 5.5	41 ± 6.6	—	—
Rearing	210 ± 29	217 ± 32	—	—
Motility	3214 ± 265	3138 ± 284	—	—

Male and female rats were tested at either 60 days (first experiment) or 90 days (second experiment) of age.
Values are expressed as median ± quartiles of the total number of counts per animal over the 30-min period in the activity cages.
No significant effects of treatment were obtained.

sions, if necessary, to maintain rats at the initial 80% free-feeding weight.

After initial shaping, the animals received 100 reinforcements per day for 3 days on a continuous reinforcement schedule (CRF) before being shifted to the discrimination schedule. Discrimination consisted of successively alternating 60-sec light-on and light-off conditions. Under the light-on condition, each bar-pressing response was reinforced. Under the light-off condition, bar presses were not reinforced. The animals were tested for 30 min per day for 7 consecutive days. Light-on was the first condition on all days.

Differential reinforcement of low rates of responding (DRL). Approximately 1 month after completing the L/D discrimination, rats were given DRL training through a successive approximation procedure using the same cages as above. In this experiment, all sessions were conducted in the lighted-box condition. The animals (the total number of rats were 36, of which nine were assigned to each group) were given a CRF schedule on one day. Then it was necessary for the rats to withhold a bar-pressing response in order to be reinforced; that is, they were introduced to the DRL schedule in which only responses that had been withheld for a given length of time were rewarded. The time the bar pressing had to be withheld was successively increased from 1 sec with increments of about 2.5 secs per session until DRL-20 was in effect where at least 20 secs must have elapsed since the last bar press in order to lead to access to the reinforcer. After this, 14 days of DRL-20 training followed. As indicated earlier, supplementary feeding was done with the regular diet and the reinforcer was the egg mixture described. Animals were trained once daily, 5 days per week.

Swim maze. The swim-maze test was carried out as described by Morris (11), with minor modifications. The swim maze was a circular bath (diameter 140 cm) thermostatically controlled at 25°C. The bath included a platform 1 cm below the water level. Milk powder was added to the water to prevent the rats from seeing the platform. Before testing, all rats were given swim training, for which the platform was removed and the animals allowed to swim for 60 secs. During the training, the swimming ability of each rat was recorded.

After the platform had been placed at a particular position within the pool, each animal had five trials on 3 consecutive days. In each trial, the rats were placed at the same point in the bath and allowed to swim around to find the platform and escape from the water onto it. If the rat failed to find the platform within 65 secs, it was put there manually. On reaching the platform, the rats were allowed to remain on it for 30 secs (intertrail interval) before being placed in the water again for next trial. After the fifth trial, each animal was placed in a cage with a blow dryer that blew warm air toward it. Thus care was taken that each animal was allowed to dry itself completely before being replaced in its home cage. In addition to a drawing of the swim path of each rat on each trial, two measures of performance were recorded: 1) the time required to reach and climb onto the platform and 2) the number of failures where the animal did not reach the platform during the 65-sec swimming period.

Statistical Analysis

Data from the mothers and litters before weaning were analyzed statistically on a litter basis by means of group, and the groups were examined statistically by means of the nonparametric Wilcoxon rank test (12) and a two-tailed criterion. After weaning, individual pups were used as a statistical base and the results evaluated by a two-way analyses of variance (ANOVA). When group sizes were unequal, nonparametric Kruskal-Wallis or Mann-Whitney *U*-tests were used (13). Parametric Tukey's HSD test was used in

Table 3. Conditioned Avoidance Responding (CAR) after Prenatal Lidocaine Exposure

	Control males (n = 6)	Lidocaine males (n = 10)	Control females (n = 6)	Lidocaine females (n = 10)
Avoidance responses				
Day 61	3 ± 6	2 ± 1	10 ± 11	1 ± 2
Day 62	10 ± 11	7 ± 6	19 ± 11	8 ± 10
Day 63	9 ± 9	16 ± 7	23 ± 10	21 ± 10
Day 64	14 ± 8	14 ± 9	26 ± 6	24 ± 9
Day 65	22 ± 7	19 ± 8	25 ± 5	26 ± 5
Escape responses				
Day 61	13 ± 5	20 ± 6	14 ± 10	21 ± 6
Day 62	15 ± 7	19 ± 6	12 ± 4	11 ± 7
Day 63	14 ± 6	10 ± 4	5 ± 6	9 ± 8
Day 64	16 ± 8	17 ± 9	5 ± 6	10 ± 11
Day 65	8 ± 7	12 ± 9	6 ± 5	9 ± 12
Failures to respond				
Day 61	9 ± 9	5 ± 5	1 ± 4	3 ± 6
Day 62	4 ± 5	3 ± 3	1 ± 3	2 ± 4
Day 63	2 ± 6	3 ± 4	2 ± 4	1 ± 2
Day 64	0	0	0	0
Day 65	0	0	0	0

Male and female rats were tested at 61–65 days of age.
Values are expressed as medians ± quartiles.

the evaluation of negative geotaxis, L/D discrimination, and DRL (14).

Results

Clinical Observations of Mother Rats

No signs of dysfunction were observed that could be related to the treatment with the test compound. There was no difference in mean body weight gain, mean food consumption, or water consumption between the test and control groups. Duration of gestation had the same distribution between 21 and 22 days in both groups.

Clinical Observations of the Litters

No intergroup differences in litter size or pup loss were observed, nor could intergroup differences in mean pup weights be detected at birth or on days 7 and 21. All pups in both groups showed unfolded pinnas on day 4 and opened eyes on day 17. Tooth eruption occurred on days 11 or 12 in all pups, though on day 12 in two more litters in the control group than in the lidocaine-treated group.

Behavioral Studies on the Pups

Negative geotaxis. There was no difference in latencies between the two groups, and no effect of lidocaine treatment (Table 1).

Table 4. Tail-Flick, Hot-Plate, and Shock-Titration Responding

	Control males	Lidocaine males	Control females	Lidocaine females
Tail-flick test (sec)				
Median	4.20	4.20	4.25	4.10
Q	± 0.53	± 0.45	± 0.38	± 0.43
Hot-plate test (sec)				
Median	5.0	5.0	5.0	6.0
Q	± 1.0	± 1.5	± 0.5	± 1.0
Shock-titration test (μA)				
Median	225	250	162.5	175
Q	± 25	± 50	± 25	± 13

Male and female rats were tested at 70 days of age on all three tests of nociception.

Female rats showed significantly lower shock thresholds. No significant effect of treatment was obtained.

Activity. 1) Locomotion: Locomotion counts showed no statistically significant differences between the groups. Males from lidocaine-treated mothers showed slightly more counts than controls, and in females the counts were less than in controls. 2) Rearing: No statistically significant differences between the groups were recorded. Lidocaine-treated males showed slightly more counts than control animals, but females less. 3) Motility: No statistically significant difference was recorded. Lidocaine-treated animals of both sexes showed slightly more counts than their respective controls (Table 2).

Conditioned avoidance responding. Lidocaine had no statistically significant effect on conditioned avoidance responding (CAR) in either sex. Pups of both groups reached a very good level of responding, although the performance of female rats was slightly but not significantly better than that of males. Percent CARs during the fifth and final sessions were control males 73%, lidocaine males 63%, control females 82%, and lidocaine females 87% (Table 3).

Tests of nociception. Perinatal lidocaine treatment had no effect in any of the tests. There was, however, a significant sex difference in the shock-titration test (Mann-Whitney U-test, $P < 0.01$), female rats showing flinch–jump responses at significantly lower shock intensities than male rats, regardless of treatment (Table 4).

Light/dark discrimination. Lidocaine-treated males tended to perform slightly better in the L/D discrimination task than controls, but not significantly so; that is, the lidocaine males made consistently more bar pressures during the light period. During the dark

Table 5. Group Mean Values for Response Latency in the Light/Dark Discrimination Task after Prenatal Lidocaine Exposure

	Control males	Lidocaine males	Control females	Lidocaine females
Day 1	10.4 ± 2.6	8.5 ± 3.1	5.0 ± 1.2	8.4 ± 2.0
Day 2	9.0 ± 2.1	8.3 ± 2.7	7.7 ± 2.5	7.7 ± 2.1
Day 3	21.1 ± 11.6	4.9 ± 1.5	14.5 ± 3.2	12.7 ± 3.9
Day 4	11.6 ± 3.9	2.7 ± 0.5	4.8 ± 1.1	5.4 ± 2.9
Day 5	7.1 ± 2.1	5.1 ± 2.3	3.1 ± 0.5	4.4 ± 0.8
Day 6	9.4 ± 4.5	6.1 ± 3.0	4.9 ± 1.7	4.6 ± 0.8
Day 7	18.4 ± 12.2	11.9 ± 6.5	3.0 ± 0.5	2.4 ± 0.4
Mean over period	12.4	6.8	6.1	6.5

Male and female rats were tested at age 65–70 days.
Values are expressed as mean ± SEM.
t-Test: control males vs lidocaine males ($t = 2.33$, $P < 0.01$) for the mean over all 7 days.

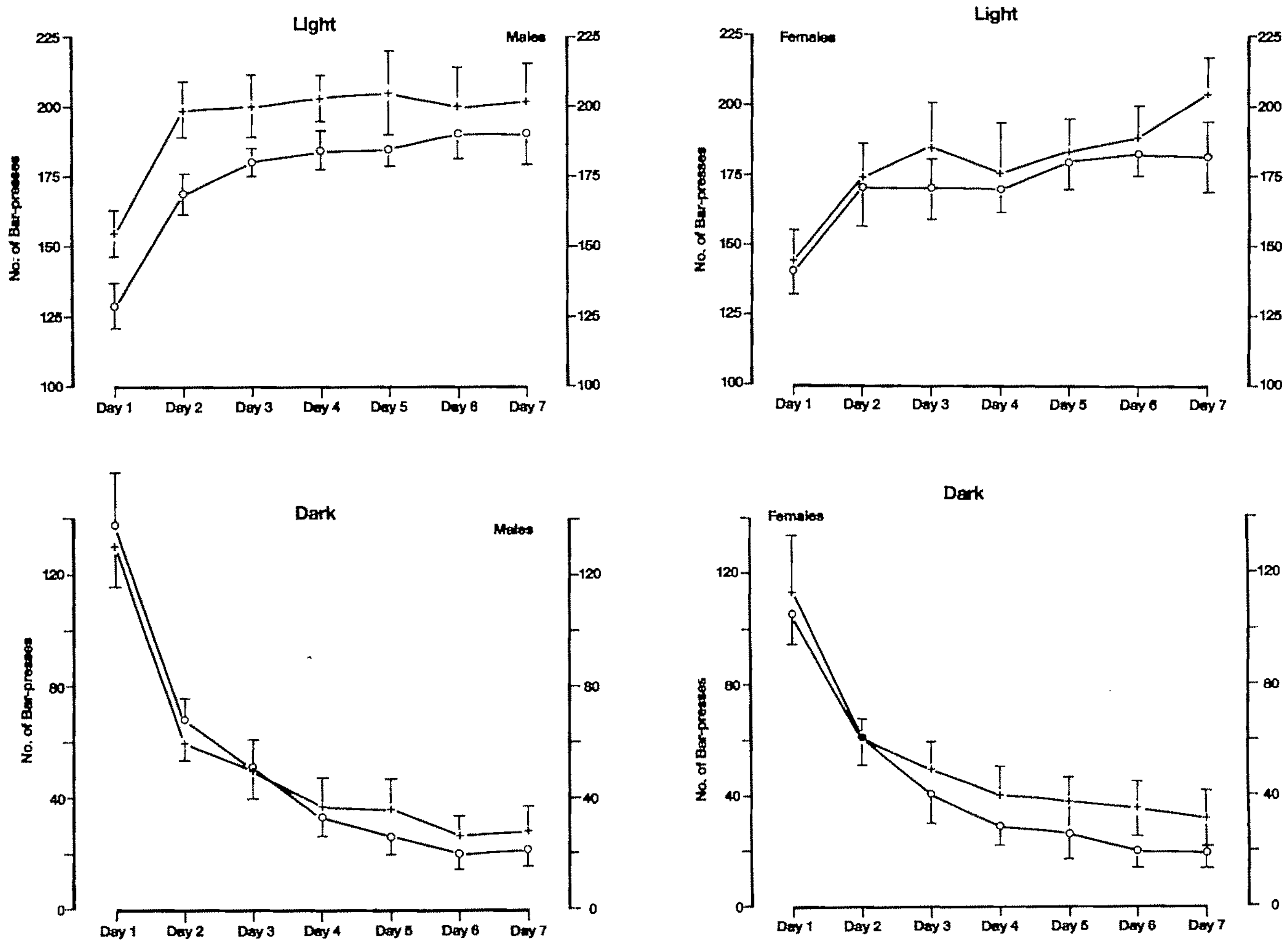

Figure 1. Light/dark discrimination test. Lidocaine and control rats were reinforced for responding during the light phase but not during the dark phase. O—O, control and + — +, lidocaine-treated animals. Differences between controls and treated animals in either males or females were not statistically significant.

period, no consistent trends emerged. For the latency data (Table 5), there was a significant group effect [F(323) = 3.5], resulting from a significant longer latency by the control males over all 7 days. No difference was observed in the female rats (Fig. 1).

Differential reinforcement of low rates of responding. Male control rats showed a significantly higher rate of responding and thus obtained a lower number of reinforcements than the males in the lidocaine-treated group. Thus ANOVA showed a significant group ef-

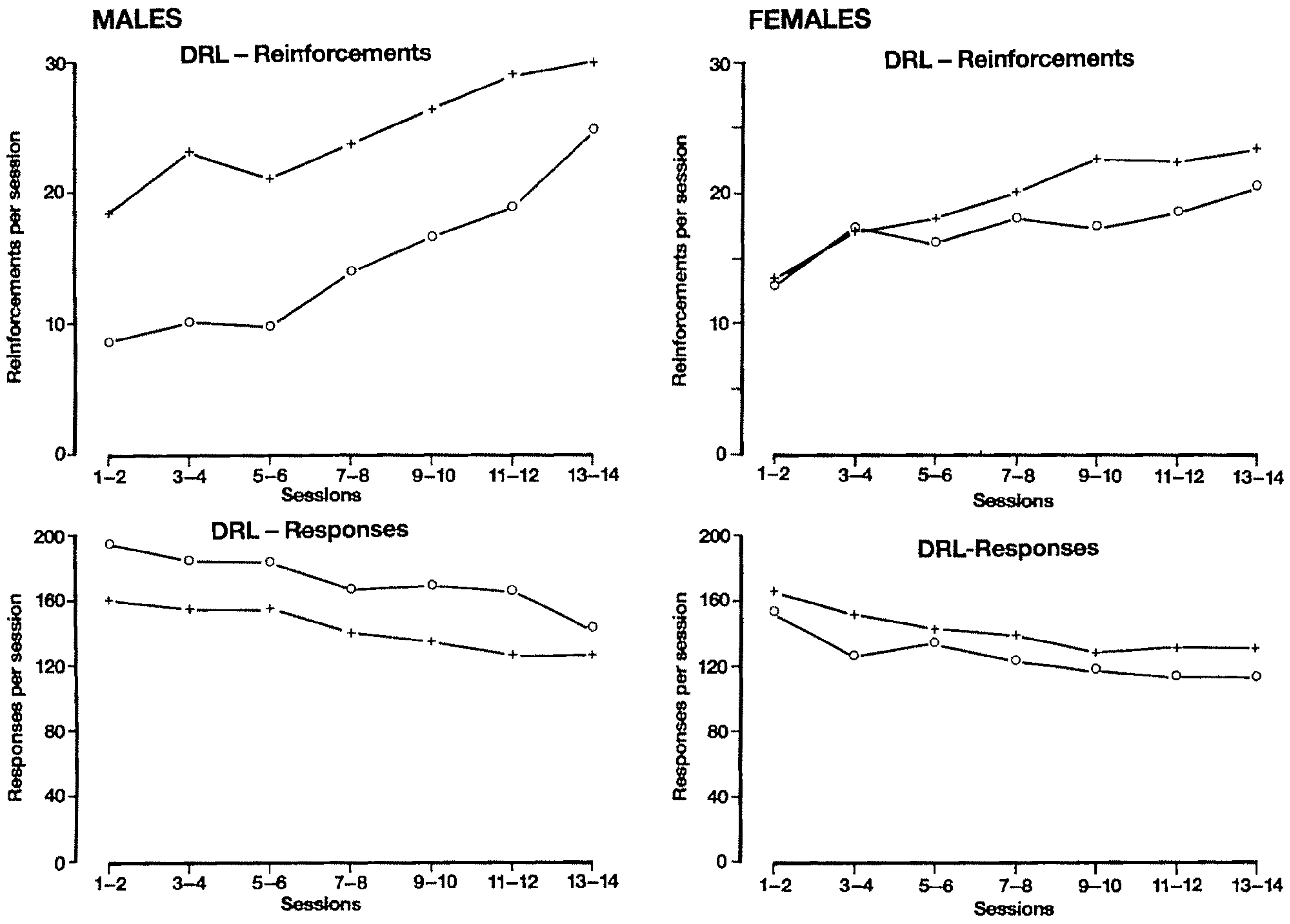

Figure 2. DRL-20, reinforcements and responses. Lidocaine an control rats were reinforced only when responding had been with held for a 20-sec period. O—O, control and +—+, lidocaine-treate animals. Control males showed a significantly higher rate of re sponding, leading to a lower number of reinforcements. This ma be considered to be a random effect of population.

fect [F(3,209) = 7.1], resulting from a greater number of reinforcements in lidocaine males than in control males. In female rats, there was no significant difference between the groups, but a clear trend by which the lidocaine rats received more reinforcements (Fig. 2). The mean number of reinforcements by each group over all 7 days was as follows: lidocaine males = 24.5, control males = 14.8, lidocaine females = 19.6, control females = 17.5.

Swim maze. No differences between groups were recorded. In both groups, a reliable and consistent acquisition of the spatial orientation task and a good swimming ability were observed (Table 6).

Discussion

The present findings show no evidence of behavioral deficits or consistent alterations as a result of prenatal treatment with lidocaine (6 mg/kg) on gestation days 10 and 11. The results can be summarized as follows:

1. Development of negative geotaxis was essentially the same in the offspring of both saline- and lidocaine-treated dams, whether the pups were mal or female.
2. No significant differences in spontaneous moto activity emerged, nor were there any consisten trends.
3. All four groups (control males and females; lidocaine males and females) showed good CAR ac quisition, though female rats generally performe better than males.
4. Females also demonstrated lower shock threshold than male rats but no differences were apparen in the hot-plate and tail-flick tests. Neither CA acquisition nor pain sensitivity was affected by pre natal lidocaine.
5. Although lidocaine males were slightly better tha

Table 6. Swim Maze Acquisition after Prenatal Lidocaine Exposure

	Control	Lidocaine
Day 91		
Latency ± SEM	40 ± 10	46 ± 2
≥65[a]	2 ± 1	3 ± 0.5
Day 92		
Latency ± SEM	17 ± 5	17 ± 5.5
≥65[a]	0 ± 0.5	0 ± 0.25
Day 93		
Latency ± SEM	10 ± 4.5	8 ± 2
≥65[a]	0	0

Male rats were tested at age 91–93 days.
Values are expressed as means ± SEM.
[a] ≥65 = number of trials within a session during which the rat failed to locate the platform over the 65-sec swim period.

control males on the L/D discrimination task, the differences were not statistically significant.

6. The DRL task was associated with a significantly better withholding response in lidocaine males than in control males, as a result of which the lidocaine males received significantly more reinforcements; the female rats demonstrated the same trend, lidocaine females receiving slightly though nonsignificantly more reinforcements. It is interesting to note that whereas control males were comparable to control females, the lidocaine males performed consistently better than lidocaine females. It cannot be argued that lidocaine males withheld responding better than the controls as a result of some type of "response suppression" since the same rats produced more bar presses during the reinforced light condition of the L/D discrimination test. It is possible that the better performance of the lidocaine males is a random effect of population; that is, the rats in that particular group of male rats simply adapted more suitably to the operant schedule.
7. Finally, there was no effect of lidocaine treatment on the swim maze task in which both lidocaine and control rats learned to locate the submerged platform quite rapidly.

Previous findings have suggested a difference in the performance of cognitive tasks by newborn babies of mothers given local anesthetics during pregnancy as compared with the babies of untreated mothers (1), and the recent paper by Smith et al. (4) indicated the possibility of a deficit in the performance of the L/D discrimination task by offspring of lidocaine-treated dams. In the present study, no evidence of a discrimination deficit in a similar operant task was seen; if anything, lidocaine males tended to perform better than controls. These investigators also obtained alterations of negative geotaxis and motoractivity; neither of these effects were produced in the present investigation. In a second study (15), it was found that the offspring of lidocaine rats were deficient in the acquisition of a water maze task and showed longer tail-flick latencies, but neither of these effects appear to be confirmed by the present investigation. It is interesting to note that the most taxing cognitive task employed, the DRL-20 schedule, resulted in a significantly better performance by lidocaine male rats. However, it would be foolhardy to suggest that this effect was due to prenatal treatment. It is most likely that the individuals composing this group were quicker to adapt from a continuous reinforcement schedule to the DRL-20 schedule for reasons unrelated to the treatment. The most consistent finding obtained here is that the performance of female animals differed in several instances from males, but this result was neither novel nor unexpected.

In conclusion, the results demonstrate that even two injections of lidocaine to pregnant rats on consecutive days fail to affect the later development of the behavioral repertoire and cognitive abilities of male and female offspring.

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Is Fentanyl an Anesthetic in the Dog?

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The authors used the absence of vocalization and movement during application of a hemostat clamped to the first ratchet at the base of the tail as an indication of anesthesia for evaluation of the anesthetic properties of fentanyl in the dog. Eighty-six unpremedicated, unrestrained, untrained mongrel dogs were given one of eight doses of fentanyl citrate (125, 250, 500, 750, 1000, 1500, 2000, and 3000 μg/kg) as a single intravenous bolus injection. Dogs breathed spontaneously without oxygen supplementation. Anesthesia was assessed every 5 min until absence of anesthesia was recorded for two consecutive evaluations. Venous plasma samples were obtained in two or three dogs receiving each of the doses of fentanyl 5 min after fentanyl injection and again when application of the tail clamp elicited either vocalization or movement (positive response). Fentanyl resulted in recumbency in all animals except two receiving 125 μg/kg. Although all doses of fentanyl produced anesthesia in at least one animal 5 min after injection, the duration of anesthesia was short, responses unpredictable, and anesthesia achieved in all animals only with a dose of 3000 μg/kg. Increasing doses of fentanyl resulted in higher plasma fentanyl concentrations 5 min after injection and at the time of the first positive response to tail clamp but there was great variability. All doses of fentanyl caused statistically significant decreases in heart and respiratory rates but none produced apnea or a Pa$_{CO_2}$ higher than 67 mm Hg. All dogs survived without sequelae. The data demonstrate that fentanyl can produce anesthesia in the dog but that requirements vary enormously and are extremely high in some animals and duration is short.

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl. ANALGESICS—fentanyl.

A high dose of fentanyl (50–150 μg/kg) with or without sedative or hypnotic supplements is frequently used for anesthesia in patients undergoing cardiac, vascular, and other long or difficult operations (1,2). The popularity of fentanyl "anesthesia" for these patients has resulted in numerous recipes of administration and has produced a potpourri of clinical findings, problems, opinions, and controversies (2). One of the most important of these is whether fentanyl, or any opioid, should be considered an anesthetic (3). To explore this question, many investigators have used animal models, chiefly the dog and rat, for their experiments (4,5). Our experience with opioids in a variety of mammals suggests that most, including the dog, are not good animal models for opioid evaluation because dosage requirements and responses are so different than in humans (6,7). The objective of this study was to determine whether fentanyl was capable of producing anesthesia in the dog. In addition, we attempted to calculate the anesthetic ED_{50} and to measure the duration of anesthesia after a single, intravenous bolus injection of fentanyl.

Methods

Eighty-six healthy mongrel dogs weighing 20–30 kg, served as the experimental subjects. The dogs were unpremedicated, unrestrained, untrained, used only once, and had food removed at 4:00 PM the day before study and water removed 2 hr prior to study. Experiments were scheduled to begin between 9 and 10 AM and dogs were randomly allocated to receive one of eight doses of fentanyl citrate (125, 250, 500, 750, 1000, 1500, 2000, 3000 μg/kg) as a single intravenous bolus. These eight doses are equivalent to 80, 159, 318, 477, 637, 955, 1273, and 1910 μg/kg of fentanyl as the base.

Upon arrival in the laboratory, each animal had an 18-gauge plastic catheter with a heparin lock inserted into an extremity vein. After this, control heart and respiratory rates (via auscultation and observation of the chest and abdomen) were recorded and a femoral

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Table 1. Percent Dogs Anesthetized (Negative Response to Tail Clamp) According to Dose and Time after Injection of Fentanyl

Dose[a] (μg/kg)	Minutes after injection					
	5[b]	15[b]	30[b]	60[b]	90	120
125	10	0	0	0	0	0
250	80	50	20	0	0	0
500	50	30	20	10	0	0
750	80	60	60	20	10	10
1000	60	20	10	0	0	0
1500	60	40	30	10	0	0
2000	85	62	39	8	8	0
3000	100	77	54	46	23	8

[a] Fentanyl as the citrate salt.

[b] Test for linear trends $P < 0.005$.

arterial blood sample (2 ml) obtained (via percutaneous puncture) for measurement of Pa_{O_2}, Pa_{CO_2}, and pHa using a Radiometer Copenhagen ABL-1 blood gas machine. After a 5-min stabilization period, one of the eight doses of fentanyl was rapidly injected intravenously. The dogs were not intubated, received no respiratory assistance, and breathed room air ($F_{I}O_2 = 0.21$) throughout the study. Heart and respiratory rates were recorded every 5 min for the first 30 min after injection of fentanyl and then every 15 min for the next 90 min. Additional arterial blood samples for blood gas analysis were obtained before (as mentioned above) and every 15 min after injection of fentanyl for 1 hr and every 30 min for the second hour (or until the animal resumed a standing position).

Anesthesia was defined as the absence of purposeful movement or vocalization to the application of a 10-inch hemostat clamped to the first ratchet at (or as close as possible to) the base of the tail for 30 sec. The tail was moved continuously with the hemostat for the duration of stimulation. After injection of fentanyl, time to onset and duration of ataxia and recumbency were recorded for each dog. Ataxia was defined as the inability to stand on all four extremities without support or the presence of an abnormal (stumbling) gait. After becoming fully recumbent, anesthesia was assessed every 5 min for the first 15 min after fentanyl injection and every 15 min thereafter until positive responses (absence of anesthesia) were recorded for two consecutive evaluations.

Time-related anesthetic ED_{50} values were calculated 5 and 15 min after fentanyl administration using stepwise logistic regression. A time-related anesthetic ED_{50} is defined as the dose of fentanyl necessary to prevent movement in 50% of animals at a specific time after injection of the drug. Thus, a 5-min ED_{50} is the dose preventing movement in 50% of animals 5 min after injection.

Table 2. Dose, Plasma Fentanyl Concentration, and Tail Clamp Response 5 Min after Injection

Dose (μg/kg)	Plasma concentration (ng/ml)	Tail clamp response[a]
125	44	+
125	47	+
250	25	–
250	82	–
250	110	–
500	132	–
500	166	+
750	110	–
750	230	+
750	502	–
1000	187	–
1000	198	+
1500	272	–
1500	296	+
1500	323	+
2000	390	–
2000	465	+
2000	760	–
3000	820	–
3000	695	–
3000	850	–

[a] + = positive response (movement) upon tail clamp; – = negative response (no movement) upon tail clamp.

Venous blood samples (7.0 ml) were obtained from two or three dogs in each fentanyl dosage group for analysis of plasma fentanyl concentrations. Blood samples were obtained 5 min after injection of fentanyl and when the response to tail clamp first became positive. Plasma was separated by centrifugation and fentanyl (concentrations expressed as the base) extracted with a mixture of hexane and ethanol (volume ratio 19:1). Plasma fentanyl was measured by a capillary gas chromatography–chemical ionization mass spectrometric (CGC/CIMS) method that employed a Finnegan 4500 gas chromatograph/mass spectrometer linked to a Finnegan INCOS data system. Chromatographic separation was achieved using hydrogen as a carrier gas (60–100 cm/sec) and a DB5-15W column with a 1-μM film thickness. Methane and ammonia were the reagent gases for the mass spectrometer. The complete venous blood sample was injected and injection temperature was 265°C. Column temperature was programmed at 170°C for 0.5 min and then increased by 23°C/min to 300°C. Transfer line temperature was 230°C and ion chamber temperature 120°C. Carfentanil was used as an internal standard and the current monitored at m/z 337 for fentanyl and at m/z 395 for carfentanil. Quantitation was achieved by measuring the peak height ratio of fentanyl to carfentanil (internal standard). The lower limit of sensitivity was 0.2 ng/ml with the standard curve being linear between 2.0 and 20 ng/ml ($r^2 = 0.9996$). Higher concentrations were diluted until measured values fell between 0.2 and 20 ng/ml. The coefficient of variation at 34 ng/ml was 4.6% within each daily run and 6.0% overall.

Data were analyzed for statistical significance utilizing the BMDP statistical package of the University of California at Los Angeles in a DEC PDP 11/73 computer (BMDP Statistical Software, Department of Biomathematics, UCLA. Berkeley, CA: University of California Press, 1981.). Differences between groups at individual points in time were determined by one-way analysis of variance for overall group differences and by Bonferroni *t*-tests for individual between-group differences. Time-related changes in groups were tested by either paired or unpaired *t*-tests as appropriate. ED_{50} values were calculated by logistical regression and correlations for dose effect on anesthetic action by tests for linear trends.

Results

There were ten dogs in all dosage groups except the 2000 and 3000 μg/kg groups, which had 13 dogs each. Fentanyl produced ataxia in all dogs within 30 sec and full recumbency in all but two animals (both given 125 μg/kg) within 90–120 sec of injection. Although all doses of fentanyl produced anesthesia in at least one animal in each dosage group 5 min after injection, duration of anesthesia was short and responses variable (Tables 1 and 2). In general, increasing doses of fentanyl resulted in a higher incidence and longer duration of anesthesia ($P = 0.003$; test for linear trends; Table 1). However, anesthesia was achieved in all animals only with 3000 μg/kg of fentanyl. Even after this dose, anesthesia was short-lived as 46% of animals responded to tail clamp stimulation 30 min after injection. Calculated anesthetic ED_{50} values 5 and 15 min after fentanyl injection were 329 and 1515 μg/kg, respectively.

Increasing doses of fentanyl resulted in higher plasma fentanyl concentrations 5 min after injection (Table 2) and at the time of the first positive response to tail clamp (Table 3), but there was marked variability. Although plasma fentanyl concentrations above 500 ng/ml were always associated with anesthesia (absence of a positive response to tail clamp), concentrations as high as 465 ng/ml 5 min after injection were not. In contrast, a plasma fentanyl concentration as low as 25 ng/ml 5 min after injection resulted in no response to tail clamp in one dog receiving 125 μg/kg of the opioid.

All doses of fentanyl produced marked and statistically significant ($P < 0.005$) decreases in heart rates (Table 4). Significant depression of respiratory rate occurred 5 min after all doses and magnitude and duration were dose related (Table 5). Similarly, all doses of fentanyl significantly increased arterial CO_2 and decreased PaO_2 15 min after injection (Table 6). Animals given 1000 μg/kg or less had significantly less increase in PaCO_2 than did dogs receiving 3000 μg/kg ($P < 0.05$; Table 6). All dogs survived without sequelae.

Table 3. Time and Fentanyl Plasma Concentration at Time of the First (+) Tail Clamp

Dose (μg/kg)	Time (min) after fentanyl	Plasma concentration (ng/ml)
125	5	44
125	5	47
250	10	27
250	10	41
250	10	83
500	10	58
500	5	166
750	10	41
750	10	59
750	5	230
1000	10	112
1000	5	198
1500	5	296
1500	5	323
1500	20	116
2000	5	465
2000	15	205
2000	20	275
3000	15	390
3000	20	331
3000	60	238

Discussion

The results of this study demonstrate that while certain doses of fentanyl (125 μg/kg of fentanyl citrate) are capable of blocking somatic responses (purposeful movement) to painful stimulation in some spontaneously breathing mongrel dogs, much greater doses (3000 μg/kg) are necessary to ensure nonresponsiveness in all animals. Furthermore, the data indicate that as an anesthetic in the dog, fentanyl is short-acting even after very large doses. In addition, large doses of fentanyl are not associated with respiratory arrest or profound changes in arterial blood gas tensions in the dog, although respiratory depression is clearly evident with all doses of the opioid. Although respiratory depression was dose dependent in this study, maximal decreases in heart rate occurred after 125 μg/kg or more. Our findings also show that increasing doses of fentanyl result in increased plasma

Table 4. Heart Rate (Beats/Min) before and at Various Times (Min) after Fentanyl (Mean ± SEM)

Fentanyl (μg/kg)	Before	5	15	30	60	90	120
125	102 ± 7	54 ± 5^a	59 ± 7^a	66 ± 9^a	64 ± 6^a	72 ± 16	80 ± 24
250	100 ± 5	54 ± 3^a	58 ± 4^a	64 ± 3^a	63 ± 6^a	62 ± 5^a	81 ± 11
500	86 ± 3	44 ± 4^a	48 ± 4^a	51 ± 4^a	52 ± 3^a	54 ± 3^a	61 ± 4^a
750	109 ± 7	51 ± 5^a	51 ± 3^a	58 ± 5^a	54 ± 2^a	54 ± 2^a	64 ± 3^a
1000	113 ± 8	57 ± 3^a	57 ± 1^a	59 ± 3^a	61 ± 3^a	63 ± 4^a	66 ± 5^a
1500	104 ± 5	50 ± 5^a	51 ± 3^a	48 ± 2^a	50 ± 2^a	50 ± 3^a	54 ± 4^a
2000	127 ± 14	59 ± 5^a	56 ± 3^a	59 ± 7^a	54 ± 4^a	58 ± 5^a	68 ± 10^a
3000	93 ± 5	57 ± 4^a	56 ± 3^a	58 ± 4^a	54 ± 2^a	57 ± 4^a	60 ± 4^a

See results for explanation.

[a] $P < 0.05$ compared with baseline values.

Table 5. Respiratory Rate (Breaths/Min) before and at Various Times (Min) after Fentanyl (Mean ± SEM)

Fentanyl (μg/kg)	Before	5	15	30	60	90	120
125	117 ± 24	29 ± 9^a	120 ± 22	124 ± 21	131 ± 19	107 ± 48	75 ± 45
250	78 ± 20	16 ± 4^a	42 ± 12	63 ± 16	74 ± 19	58 ± 17	55 ± 25
500	60 ± 18	16 ± 7^a	33 ± 14	47 ± 15	59 ± 20	54 ± 20	44 ± 16
750	139 ± 25	17 ± 6^a	28 ± 9^a	38 ± 11^a	31 ± 8^a	38 ± 12^a	24 ± 4^a
1000	130 ± 18	21 ± 4^a	34 ± 7^a	50 ± 15^a	84 ± 21	60 ± 15^a	53 ± 14^a
1500	72 ± 16	10 ± 2^a	16 ± 8^a	22 ± 9^a	23 ± 10^a	23 ± 9^a	22 ± 8^a
2000	110 ± 20	11 ± 4^a	15 ± 3^a	29 ± 7^a	28 ± 6^a	21 ± 3^a	34 ± 13^a
3000	63 ± 22	8 ± 1^a	10 ± 2^a	23 ± 7^a	36 ± 12	43 ± 15	27 ± 7^a

See results for explanation.

[a] Data points statistically different from their respective baseline values, $P < 0.05$.

fentanyl concentrations not only shortly after injection but also at the time of the first positive response to painful stimulation; however, again there was much variability.

Our results and conclusions are different than those of two other recent reports addressing the same subject. Arndt et al. (5) administered a total of 167.5 μg/kg of fentanyl in five incremental intravenous boluses at 5-min intervals to spontaneously breathing dogs. Although they observed similar degrees of respiratory depression as we did in this study, they also found that fentanyl was capable of totally blocking all somatic and cardiovascular responses to painful tail clamp stimulation after as little as 67.5 μg/kg (producing a plasma fentanyl concentration of 31 ± 0.8 ng/ml). They also observed that additional fentanyl (100 μg/kg, producing a plasma concentration of 453 ± 2.3 ng/ml) caused no further cardiovascular or respiratory change. As a result, they concluded that the respiratory, cardiovascular, and analgesic effects of fentanyl occur in parallel and reach a maximum at a plasma concentration of 30 ng/ml. In contrast, Murphy and Hug (4) attempted to achieve a plasma concentration of fentanyl that would totally eliminate the need for enflurane to block somatic responses to tail clamp stimulation in mechanically ventilated dogs anesthetized with enflurane. They administered up to 270 μg/kg of fentanyl as a loading dose and maintained plasma concentrations of fentanyl as high as 97 ± 32 ng/ml with a continuous infusion of 3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. They found that these high doses produced fentanyl plasma concentrations that reduced the MAC of enflurane by 65% at most. The authors concluded that there is a ceiling to the effectiveness of fentanyl as an anesthetic in dogs.

It is unclear why there should be such different results and conclusions in our own study and these previous publications. Possible explanations for those differences could include different injection techniques (infusions or multiple small bolus injections versus a single injection), experimental subjects (trained versus untrained dogs), methods of ventilating the experimental subjects, techniques of administering and evaluating a supramaximal painful stimulus, and the use of other anesthetics (enflurane).

A number of recent reports provide evidence that continuous infusion or multiple intermittent boluses of fentanyl are associated with the onset of tolerance to fentanyl in less than 3 hr in dogs and in humans within a few hours to a few days (8–10). The rate and degree of development of tolerance to opioids seem to depend on the magnitude of the dose and, with

Table 6. Arterial Blood Gas Tensions (mm Hg) (Mean ± SEM)

Fentanyl (μg/kg)	Baseline		15 min after fentanyl		60 min after fentanyl	
	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}
125	30 ± 1	67 ± 3	41 ± 1^a	55 ± 4	40 ± 4^a	67 ± 4
250	30 ± 1	72 ± 2	41 ± 2^a	51 ± 2^a	42 ± 1^a	67 ± 3
500	30 ± 1	75 ± 1	45 ± 1^a	50 ± 3^a	49 ± 3^a	56 ± 3^a
750	28 ± 1	74 ± 1	43 ± 1^a	43 ± 1^a	45 ± 2^a	58 ± 2^a
1000	27 ± 1	71 ± 3	45 ± 1^a	43 ± 2^a	46 ± 2^a	55 ± 1^a
1500	29 ± 1	69 ± 2	47 ± 3^a	43 ± 3^a	51 ± 2^a	49 ± 2^a
2000	28 ± 1	72 ± 4	46 ± 1^a	45 ± 3^a	49 ± 1^a	55 ± 3^a
3000	30 ± 1	69 ± 3	53 ± 2^a	41 ± 1^a	51 ± 2^a	50 ± 2^a

[a] Data points statistically different from their respective baseline values ($P < 0.05$, Student's paired *t*-test).

multiple doses, the time interval between doses (11,12). Tolerance to opioids develops more rapidly when large doses are used, when intervals between doses are short enough that each succeeding dose is given before complete decay of plasma levels by the preceding dose, and with continuous infusions (11–13). Tolerance can also occur after a single large dose of an opioid (14) (often called acute tolerance) and may have been present in our study as increasing doses of fentanyl resulted in higher plasma concentrations at the time of the first positive response to tail clamp. It is interesting and perhaps quite important that, while Arndt et al. (5) administered incrementally larger doses of fentanyl, four of their five doses were small (2.5, 5, 20, and 40 μg/kg), particularly for a dog, and the entire administration period was only 20 min. In contrast, Murphy and Hug (4) used a continuous infusion of fentanyl and redetermined the MAC of enflurane 60 min after six different loading doses and continuous infusion rates. In the latter experiments, MAC determinations must have been determined over a minimum of 3 hr. Thus, it is possible that the dogs studied by Arndt et al. developed minimal or no tolerance to fentanyl whereas Murphy and Hug's animals developed tolerance because of incremental dosing and prolonged exposure. Similarly, it is possible that our dogs developed acute tolerance because of the large doses of fentanyl employed.

The effect of using trained (Arndt et al.) or untrained animals (Murphy and Hug and ourselves) is unclear. Some reports indicate that wild and untrained mammals require significantly higher doses of opioids and other compounds for immobilization or anesthesia than tame, trained, or hand-raised (vs free-ranging) animals of the same species (15). Equally unclear are the influences of other compounds (enflurane in the study of Murphy and Hug) and acid-base changes (secondary to the absence of mechanical ventilation with subsequent CO_2 accumulation in the dogs studied by Arndt et al. and by us) on the results. A recent study indicates that inhalation agents may counteract the analgesic (anesthetic) effects of opioids (16). The effects of acid-base changes on delivery and penetration of fentanyl into the central nervous system are complicated and difficult to interpret. However, it would appear that hypercarbia, by decreasing the lipid solubility and unionized fraction of fentanyl in the blood, would decrease brain penetration (17). Also, respiratory acidosis appears to enhance washout of fentanyl from the brain (increased cerebral blood flow), as well as the circulatory redistribution of fentanyl (17). These effects, depending upon the degree of hypercarbia, would lead to a more rapid loss of brain-mediated effects, e.g., negative response to tail clamp. Hypoxia, in that it increases cerebral blood flow and cardiac output, would produce similar effects.

We also believe that subtle differences in applying and interpreting tail clamp stimulation in the dog can influence the results. Arndt et al. (5,18) used a 15-cm hemostat closed either partially or fully at the base of the tail. In addition, this application was for only 1–10 sec and the hemostat was not moved. In contrast, Murphy and Hug used a "sponge stick" that was moved during 1-min clamping of the base of the tail. We used a 10-inch hemostat clamped to the first ratchet for 30 sec at the base of the tail and moved it and the tail continuously. This technique is similar to that described by Eger et al. (19) for production of supramaximal stimuli in the dog during evaluation of the MAC of inhalation anesthetics. Many of our dogs did not move during the first 15 sec of clamp application or before movement of the tail with the clamped hemostat. Whether a hemostat provides more pain than a sponge stick, and whether clamping to full ratchet or less than full ratchet, as well as time and movement, is important, was not carefully studied. However, submaximal stimuli, which do not "stress" antinociception to the maximum, may produce misleading results and conclusions about fentanyl, its ability to produce analgesia or anesthesia, and the spectrum of physiologic responses to be found.

Recent publications have suggested that some of the effects of fentanyl may be mediated by mechanisms other than opioid receptor-associated actions (20) and that the anesthetic action of fentanyl can be dissociated from its analgesic effect (21). We did indeed observe a plateau in the anesthetic effects of fentanyl (Table 1) before a further increase in the percent of dogs anesthetized (up to 100%) could be achieved (Table 1). This plateau (where doses including 250–2000 μg/kg produce similar responses to tail clamp) may be related to the difference between the plasma concentration of fentanyl required for specific receptor-mediated effects, on the one hand, and nonspecific, possibly membrane-mediated, effects, on the other. In this light, attempts to define the anesthetic capabilities of fentanyl in terms of its analgesic and/or receptor-mediated effects alone may not be fully appropriate.

Several weaknesses of this study deserve mention. Although all dogs had access to water for up to 2 hr before the study, baseline heart and respiratory rate values were variable. Dehydration was not anticipated with our feeding regimen, but it is possible that volume status varied significantly. Also, as ventilation in the dog normally serves as a heat as well as a respiratory gas exchanger, thermoregulation could have influenced respiratory rate in addition to fentanyl. Unfortunately, no attempt was made to evaluate these factors further. Differences in blood volume status and hemodynamics may have also influenced the pharmacokinetics of fentanyl, and thus MAC determinations. Furthermore, we examined the effect of a single large bolus of fentanyl. Although the effect of fentanyl is believed to be largely attributable to receptor-mediated mechanisms, we made no attempt to produce or measure a steady state of fentanyl in plasma or cerebrospinal fluid or at specific receptor sites. In fact, it is most likely that plasma fentanyl concentrations were rapidly declining throughout a significant portion of the study (first 15 min) and that the already variable nature of the effect of opioids was further multiplied by our administration and sampling schedules. The fact that there is probably a time lag between fentanyl plasma concentrations and central nervous system effect as determined by spectral edge in humans also compounds interpreting the relationship between dose and effect, especially between 5 and 15 min after drug administration (22).

Nevertheless, several important inferences can be drawn from our study. Increasing awareness and concern about the care of animals used as experimental subjects highlight the fact that dogs, the most ubiquitous research animal in anesthesia, cannot be anesthetized reliably with fentanyl (23). Other anesthetic agents should be used to ensure that dogs do not suffer when experiments produce pain in these animals.

This study also demonstrates some of the significant differences in physiology and pharmacology between humans and dogs. Most notable is the difference in the effect of fentanyl on spontaneous ventilation and the response to painful stimulation. Doses that produce profound respiratory depression, apnea, and anesthesia of significant duration (along with muscle relaxants) in human beings do none of these in the dog. On the other hand, extremely high doses of fentanyl that are never used in humans are well tolerated in the dog, with spontaneous ventilation remaining intact and anesthesia of short duration being achieved in most animals. These and other differences lead us to question how appropriate it is to apply to human beings conclusions drawn from studies, especially involving narcotics, in the dog.

In summary, our data indicate that while fentanyl, as an intravenous bolus, can block the somatic response to supramaximal painful stimulation in the dog (can produce anesthesia), requirements vary enormously and are extremely high in some animals. In contrast, most effects on heart rate are achieved at relatively low doses for the dog (125–250 μg/kg). Although most respiratory effects are produced by similar doses, larger doses (up to 3000 μg/kg) of fentanyl still depress ventilation further, although neither respiratory arrest nor severe depression occurs.

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Hypotension in Spinal Anesthesia:

A Comparison of Isobaric Tetracaine with Epinephrine and Isobaric Bupivacaine without Epinephrine

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Two isobaric spinal anesthetic solutions (bupivacaine 0.5%/20 mg without epinephrine and tetracaine 0.5%/15 mg with 0.2 mg epinephrine) were compared in a double-blind study of 60 patients. Patients were injected while in the lateral recumbent position and were immediately turned supine and horizontal. Up to 30 min after injection, no differences were found between the groups regarding segmental level of analgesia, changes in heart rate, and onset to or maximum decrease in mean arterial pressure (MAP). No correlation was found between maximum decrease in MAP and level of analgesia. At time of maximum decrease in MAP (tetracaine group − 16.7 ± 12.8% (mean + SEM), bupivacaine group −19.4 + 14.8%) the level of analgesia was significantly higher in the tetracaine group (T5–6) than in the bupivacaine group (T7–8). Hypotension occurred in five patients in the bupivacaine group and in six in the tetracaine group. Two patients in the tetracaine group (but none in the bupivacaine group) had bradycardia. Hypotension together with bradycardia was observed in one patient in the tetracaine group but in no patient in the bupivacaine group. Two patients in each group developed postlumbar puncture headache. The authors conclude that the choice of local anesthetic agent, by itself, is not the sole cause of hypotension seen with spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES—spinal.

Controversy has arisen recently concerning the comparative cardiovascular effects of tetracaine and bupivacaine when used for spinal anesthesia. In some studies no differences were found (1–3); in others, the administration of tetracaine seemed to produce a greater decrease in blood pressure (4–6). In two recent studies (4,6), hyperbaric tetracaine (with or without epinephrine) produced a more profound decrease in blood pressure than did isobaric bupivacaine when given to patients in the lateral position.

In some of these studies isobaric bupivacaine was compared with hyperbaric tetracaine with (4) and without epinephrine (2,3,6). Hyperbaric epinephrine-free solutions of both tetracaine and bupivacaine have also been compared (1,3,5). The cardiovascular effects of epinephrine containing isobaric tetracaine and isobaric bupivacaine without epinephrine have not been compared when used for spinal anesthesia.

The aim of our study was to compare isobaric tetracaine containing epinephrine with isobaric bupivacaine without epinephrine, using methods similar to those used in the study of hyperbaric tetracaine with epinephrine (4).

Materials and Methods

Sixty patients (17 women and 43 men) scheduled for surgery under spinal anesthesia were studied. The study was approved by the Institutional Review Board for Human Research at University Hospital, University of Cincinnati Medical Center, and written consent was obtained from all patients before their inclusion in the study. The patients were randomly distributed into two groups.

Patients were given an average dose of 10 mg diazepam orally 0.5–2 hr before lumbar puncture. All

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Table 1. Onset of Analgesia

Level of analgesia	Bupivacaine	Tetracaine	Level of significance
L-2	3.4 ± 0.4	2.7 ± 0.2	N.S.
T-10	8.2 ± 1.2	5.6 ± 0.7	N.S.
T-7	12.1 ± 2.4	13.3 ± 3.0	N.S.

Values are given as minutes; mean ± SEM.

were prehydrated with approximately 500 ml of crystalloid solution immediately before induction of anesthesia. Lumbar puncture was performed with a 22 or 25-g spinal needle at the L2–3, L3–4, or L4–5 interspace using a midline or paramedian approach with the patients in the lateral decubitus position. The anesthesiologist administered the local anesthetic to all patients according to a randomized code. Another investigator, unaware of which solution had been given, evaluated the blockade.

Solutions used were 3 ml of tetracaine 0.5% (15 mg) with epinephrine (0.2 mg) or 4 ml of bupivacaine 0.5% (20 mg). Neither solution contained dextrose. Presuming the specific gravity of cerebrospinal fluid to be 1.0069 ± 0.0003 (SD), the tetracaine solution was isobaric (sp gr 1.0064), and the bupivacaine solution was slightly hypobaric (sp gr 1.0059) (7). Once a free flow of clear cerebrospinal fluid was obtained, the anesthetic solution was injected at a rate of 0.2 ml/sec, the needle was then withdrawn, and the patient was immediately turned into a supine, horizontal position.

Heart rate and blood pressure were recorded before and every 5 min during anesthesia and the electrocardiogram (ECG) was continuously monitored.

The cephalad level of analgesia (loss of sensation to pin prick) was determined every 2 min for approximately 30 min after injection of the anesthetic solution. At the same time intervals that the level of analgesia was determined, the degree of motor blockade was assessed on a 0–3 scale as previously described (4).

Surgery started 30–45 min after injection. Mean duration of surgery was 1.5 hr.

Further assessments of the sensory and motor loss were made at 30-min intervals, when possible, intraoperatively and in the postoperative period until anesthesia had regressed completely. Additionally, the patients were followed-up postoperatively for complications.

Wilcoxon rank-sum test, Student's t-test, χ^2-test, and Fischer's exact test were used where appropriate. Probability (P) < 0.05 was considered statistically significant.

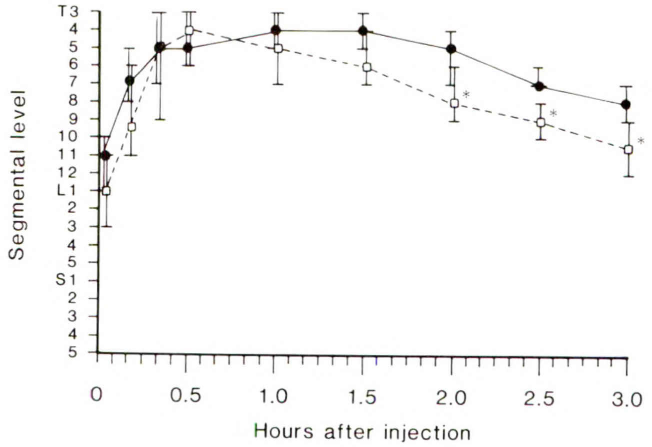

Figure 1. Segmental spread of analgesia (median values, lower/upper bounds at 95% confidence level) after administration of tetracaine (solid line) or bupivacaine (dashed line). Significant ($P < 0.05$) differences between the groups were found at 2, 2.5, and 3 hr after injection.

Results

Age, weight, and height were comparable in the two groups. No significant difference was found between bupivacaine and tetracaine with regard to time of onset of analgesia to L-2, T-10, or T-7 (Table 1). Mean time to complete motor blockade was also similar in the groups: 7 ± 1 min (mean ± SEM) for tetracaine and 8 ± 5 min for bupivacaine.

No significant differences were found between the groups with regard to rate of regression of analgesia up to 2 hr after injection. From 2 to 3 hr after injection, tetracaine sensory analgesia levels were significantly higher (Fig. 1). Total duration of analgesia was also significantly longer with tetracaine at the T-8, T-10, T-12, L-2, and L-4 segments (Table 2). Analgesia was satisfactory for surgery in all patients.

Motor blockade of the lower limbs was complete in all patients. Tetracaine produced a significantly longer duration of complete motor blockade than did bupivacaine (363 ± 18 vs 254 ± 10 min).

Cardiovascular Changes

Preanesthetic mean arterial pressure (MAP) and heart rate values were comparable in the two groups. Fifteen minutes after injection and before administration of anticholinergic drugs or vasopressors, heart rate increased 1.3 ± 3.1 and 4.7 ± 2.7%, and MAP decreased 10.0 ± 2.8 and 11.2 ± 2.2% in the bupivacaine and tetracaine groups, respectively. The difference between the groups was not statistically significant (Figs. 2 and 3).

Maximum decreases in MAP during the first 30 min after injection of the anesthetic solution were not sig-

Table 2. Duration of Analgesia

Level of analgesia	Bupivacaine	Tetracaine	Level of significance
L-4	327 ± 13	394 ± 14	$P < 0.001$
L-2	264 ± 8	334 ± 12	$P < 0.001$
T-12	214 ± 10	260 ± 12	$P < 0.01$
T-10	179 ± 11	217 ± 11	$P < 0.05$
T-8	150 ± 10	187 ± 9	$P < 0.05$

Values are given as minutes; mean ± SEM.

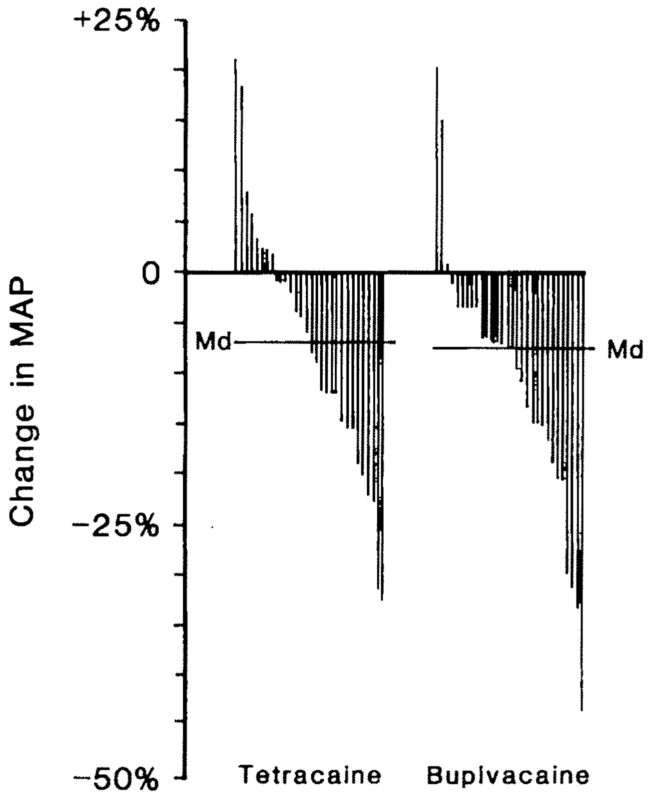

Figure 2. Ranked, individual changes in MAP 20 min after spinal administration of tetracaine and bupivacaine. Md, median value.

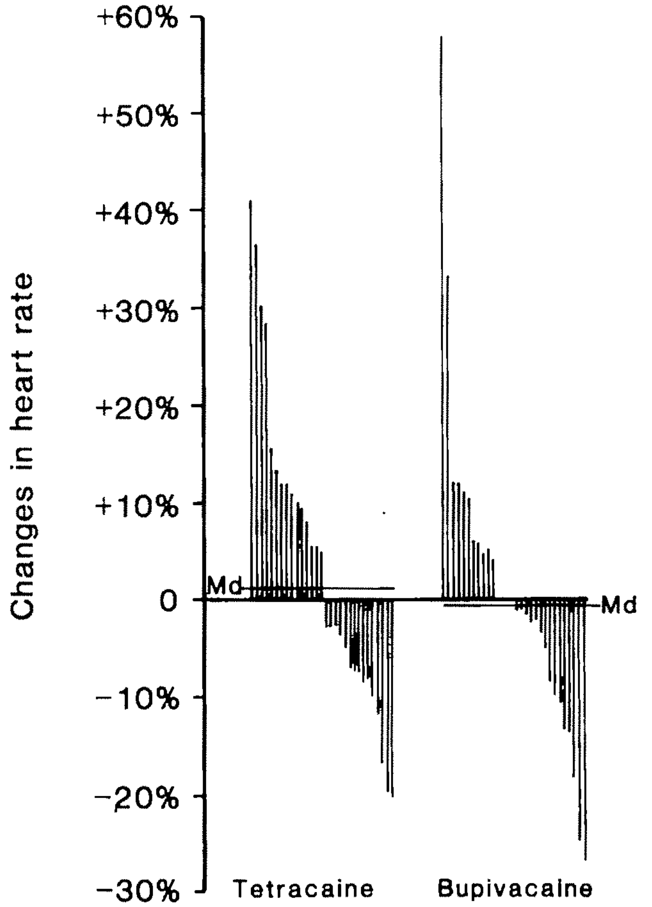

Figure 3. Ranked, individual changes in heart rate 20 min after spinal administration of tetracaine and bupivacaine. Md, median value.

nificantly different in the two groups (16.7 ± 12.8% in the tetracaine group and 19.4 ± 14.8% in the bupivacaine group) (Fig. 4). Although the time to onset of maximum decrease in MAP was not significantly different between the groups, the mean level of analgesia at the time of maximum decrease in MAP was significantly higher in the tetracaine group (T5–6) than in the bupivacaine group (T7–8).

Hypotension requiring ephedrine, phenylephrine, or both occurred in five patients in the bupivacaine group and in six in the tetracaine group. Bradycardia requiring atropine or glycopyrrolate occurred in two patients in the tetracaine group. Two patients in each group developed postlumbar puncture headache.

Discussion

In two earlier studies of similar design (4,6) using hyperbaric tetracaine with or without epinephrine, both formulations produced aa significantly greater decrease in blood pressure than did isobaric bupivacaine. No such differences were seen in our study when isobaric tetracaine was used. The results obtained with bupivacaine in those studies were similar to those obtained in our study.

It was suggested in the earlier studies (4–6) that the effects of bupivacaine and tetracaine on blood pressure could be due to different levels of the blockades and/or differences in specific gravity of the anesthetic solutions themselves. Also, because the rate for onset of analgesia was slower in the bupivacaine group (6), it was considered possible that there might have been more time available for compensatory cir-

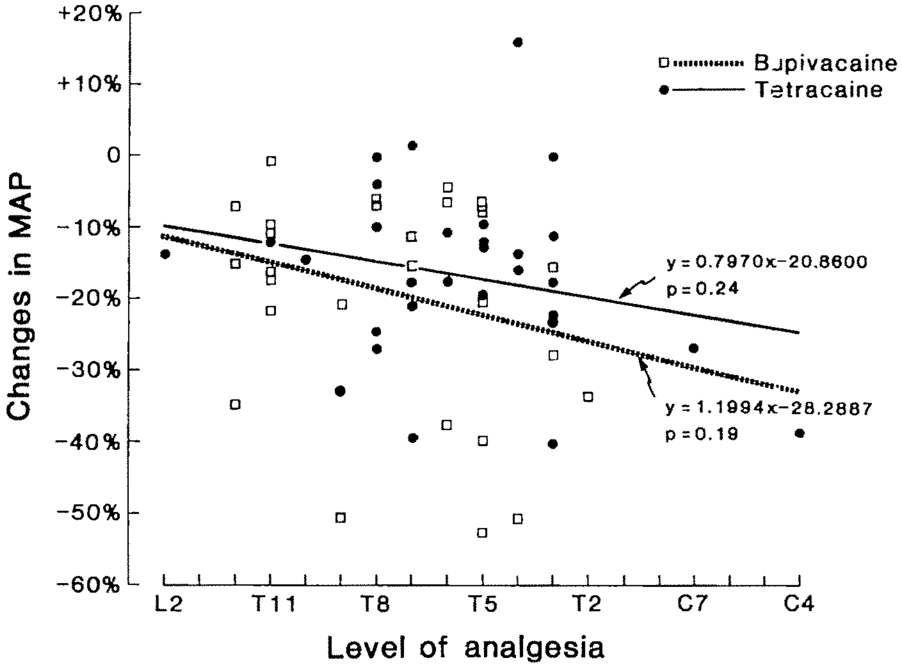

Figure 4. Maximum decrease in MAP vs level of analgesia after spinal administration of tetracaine (solid line, filled circles) and bupivacaine (dashed line, open squares). No correlation was found between maximum decrease in MAP and level of analgesia for either drug.

culatory adjustments during the onset of the bupivacaine spinal anesthesia.

Bigler et al. (5) used hyperbaric tetracaine and bupivacaine for spinal anesthesia and observed that the plasma norepinephrine levels increased significantly at the time of maximum decrease in MAP with bupivacaine but not with tetracaine spinal anesthesia. The levels of analgesia were marginally higher in the tetracaine group and it was suggested that the lower catecholamine concentration was due to a more extensive sympathetic blockade. Although it has been shown that the level of the sympathetic blockade might be lower than that of the sensory blockade when bupivacaine is used for spinal anesthesia (8), another study of lidocaine and tetracaine (9) measured higher levels of sympathetic block as compared with pinprick analgesia. Results from similar studies using isobaric bupivacaine and tetracaine solutions are warranted.

In our study the rate of onset of analgesia, the mean height of the levels of analgesia, the mean decreases in MAP, and the maximum decreases in MAP were similar in both groups. This supports the premise that slower onset of blockade allows for some degree of cardiovascular compensation.

It was also noted that the levels of analgesia at the time when the decrease in MAP was maximal were significantly higher in the tetracaine group. In spite of this significant difference in levels of analgesia, no significant difference was found with regard to maximum decreases in MAP. Nor was any correlation found between maximum decrease in MAP and level of analgesia. Consequently, there appear to be other factors controlling blood pressure changes in addition to the height of the sensory blockade. Although unproved, differences in level of sympathetic blockade may be responsible.

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The Effect of Polyethylene Glycol on Mammalian Nerve Impulses

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BENZON HT, GISSEN AJ, STRICHARTZ GR, AVRAM AJ, COVINO BG. The effect of polyethylene glycol on mammalian nerve impulses. Anesth Analg 1987;66:553–9.

Polyethylene glycol (PEG) is a polymeric compound used as a vehicle for depot steroid preparations such as methylprednisolone acetate and triamcinolone diacetate injected into the epidural or intrathecal space to relieve low back pain. There have been reports of neurodysfunction associated with these injections, and it has been postulated that the PEG vehicle is the offending agent. Studies supporting such a possibility have, however, relied upon concentrations of PEG higher than those used clinically (3%) or have used PEG in combination with other drugs. Using an in vitro rabbit sheathed-nerve preparation, we investigated the effects of a 1-hr exposure to different concentrations (3–40%) of PEG in Liley solution on the transmission of impulses of the A, B, and C nerve fibers. The 3% and 10% PEG had no effect on mean amplitudes of the compound action potentials (CAPs) nor did they significantly decrease conduction velocity. Twenty percent PEG slightly depressed and 30% markedly decreased CAPs. Both 20% and 30% PEG significantly slowed the conduction velocities of A, B, and C nerve fibers. Forty percent PEG abolished CAPs. With washout CAPs recovered to at least 80% of their baseline levels, and conduction velocities returned toward baseline levels. The pH of the Liley solution decreased with an increasing concentration of PEG, from 7.4 in the control Liley solution to 6.45 in the solution of 40% PEG. There was no evidence of an effect of the acidic pH since neither amplitudes nor conduction velocities were affected by the PEG-free Liley solution at pH 6.45 and the degrees of block were the same at pH 7.4 as at the lower pH. Experiments done on desheathed nerves showed no significant change in amplitude or conduction velocity with 3% PEG. Exposure of desheathed nerves to the 20, 30, and 40% PEG showed the same degrees of block as the sheathed nerves. We conclude that PEG, in concentration up to 40%, does not cause neurolysis.

Key Words: TOXICITY—polyethylene glycol.

Epidural (1) and intrathecal (2) steroid injections are frequently used in the treatment of low back pain. These procedures, however, are not without risks. Neurological complications of intrathecal steroids have included paraplegia, transient loss of bladder control, and adhesive arachnoiditis (3–5).

It has been postulated (6,7) that the neurolysis after intrathecal steroid injection is due to polyethylene glycol (PEG), a nonionic detergent used as vehicle for depot steroid preparations. This assumption was based on two studies (8,9). In one study, 80% propylene glycol caused destructive lesions in the sciatic nerves and brachial plexus of rabbits (8). However, the commercial preparation of the steroid contains 3%, not 80%, PEG. The other study (9) showed degenerative changes in the rat sciatic nerve after the perineural injection of the suspending vehicle of methylprednisolone acetate. This study (9) did not examine the neural effect of 3% PEG alone. In the present study, we investigated the effects of 3–40% PEG on mammalian nerve impulses.

Methods

New Zealand white rabbits, 2–3 kg in weight, were sacrificed by air embolism. The cervical vagus nerves were removed within 10–15 min and immersed in modified Liley solution aerated with 100% oxygen. The modified Liley solution consisted of NaCl, 136.8 mM; KCl, 5.0 mM; $CaCl_2$, 2.0 mM; $MgCl_2$, 1.0 mM; dextrose, 11.0 mM; Hepes buffer [4-(2-hydroxyethyl)-1-piperazine-ethane sulfonic acid], 2.53 mM. The pH was adjusted to 7.4 with 0.1 N NaOH. The nerves were cleaned of adventitia by microdissection and mounted in a nerve chamber with sheathes intact.

The design of the nerve chamber, the protocol for nerve stimulation, and the recording of the com-

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Table 1. Changes in the Compound Action Potential Amplitudes and Conduction Velocities of A Fibers Exposed to Different Concentrations of PEG in Sheathed-Nerve Preparations

PEG concentration (%)	Amplitude (mV) changes[a]	Conduction velocity (m/sec) changes[a]
0	98 ± 15 → 110 ± 12	37 ± 4.3 → 35 ± 4.7
3	95 ± 9 → 102 ± 12	39.9 ± 3.7 → 38 ± 2.5
10	94 ± 23 → 97 ± 25	37.9 ± 5.4 → 35.4 ± 5.8
20	98 ± 13 → 90 ± 19	39.4 ± 4.2 → 34.3 ± 4.8[b]
30	101 ± 22 → 76 ± 13[b]	38.7 ± 3.0 → 28.4 ± 5.6[b]
40	83 ± 14 → 0 ± 0[b]	39.2 ± 2.5 → [b,c]

[a] Mean ± SD.

[b] $P < 0.05$.

[c] Could not be determined; block was complete.

pound action potentials have been described previously (10). In brief, a 1.0-cm segment of the nerve between the stimulating and recording electrodes was stimulated with a twin-channel square-wave generator (Grass S48, Grass Instrument Co., Quincy, Mass.) via isolation units (Grass SIU 5). The stimulus durations were 0.05 ms for A fibers, 0.1 ms for B fibers, and 1 ms for C fibers. Stimulus intensities were adjusted separately for the A, B, and C fibers so as to obtain the maximum amplitude of the compound action potentials. The nerve signals were amplified 50 × (Ms model A differential electrometer, Metametrics, Carlisle, Mass.) and the compound action potentials were displayed on storage oscilloscopes (Tektronic 5113, Tektronix Inc., Beaverton, OR). The nerve fibers were identified by their conduction velocities: A fibers conduct at 25–50 m/sec, B fibers at 5–15 m/sec, and C fibers at less than 2 m/sec (10).

The nerves were randomly assigned to one of the following groups, five nerves per group: group I—control, no PEG; group II—3% PEG; group III—10% PEG; group IV—20% PEG; group V—30% PEG; and group VI—40% PEG. Randomization was accomplished with a random number table.

In each experiment, a baseline period of 30 min assured nerve function stability, during which time the modified Liley solution perfused the nerve at 0.4 ml/min. After 30 min, in the experimental groups (groups II–VI), Liley solution containing either 3, 10, 20, 30, or 40% PEG (polyethylene glycol 3350, Fisher Scientific Products, Fairlawn, NJ.) perfused the nerve at 0.15 ml/min for 1 hr. The nerves were then washed with the Liley solution at 0.4 ml/min for 2 hr or until 80% of the baseline amplitude of the compound action potential (CAP) was attained. In the control group, the Liley solution perfused the nerve throughout the study. Amplitude and latency of the CAP of the different fibers were measured from the oscilloscope face and recorded every 5 min during the study. All experiments were performed at room temperature (20–22°C).

The amplitudes and latencies of the A, B, and C fibers at the end of the 30 min (just before drug addition) were considered to be baseline values. A two-factor analysis of variance with repeat measures on one factor initially analyzed the data. Postexposure comparisons with baseline values were made with Bonferroni correction of the paired Student's *t*-test while comparisons between groups at the various observation times were made with Bonferroni correction of the unpaired Student's *t*-test (11). Values of $P < 0.05$ were considered statistically significant.

The pH of the modified Liley solution decreased with increasing PEG concentration, from a baseline pH of 7.4 to 7.38 with the addition of 3% PEG, 7.30 with the 10% PEG, 6.95 with the 20% PEG, 6.75 with the 30% PEG, and 6.45 with the 40% PEG. To investigate the role of pH, we performed experiments in which the pH of the Liley solution was decreased to 6.45 by the addition of 0.1 N HCl. Experiments were also carried out wherein the pH of the 20–40% PEG in Liley solution was increased to 7.4 with 0.1 N NaOH (one experiment per PEG concentration).

Experiments were also performed on desheathed nerves since they better represent intrathecal injection. Nerves were exposed to Liley solution with or without 3% PEG. There were five nerves in each group; the sequence of experiments was randomized. The methods and analysis of data were the same as in the sheathed-nerve experiments.

We also investigated the ability of the higher concentrations of PEG to pass through the nerve sheath. Desheathed nerves were exposed to 20–40% PEG, at pH 6.95–6.45, for 1 hr (one experiment per PEG concentration). The degree of amplitude depression and conduction velocity slowing were compared with the experiments on sheathed nerves.

Results

We compared the values at 30 min (baseline) with the results at the end of 60 min of drug exposure. The

Table 2. Changes in the Compound Action Potential Amplitudes and Conduction Velocities of B Fibers Exposed to Different Concentrations of PEG in Sheathed-Nerve Preparations

PEG concentration (%)	Amplitude (mV) changes^a	Conduction velocity (m/sec) changes^a
0	48 ± 16 → 49 ± 14	9.9 ± 1.0 → 9.4 ± 0.9
3	56 ± 17 → 60 ± 18	10.6 ± 1.1 → 10.1 ± 1.0
10	45 ± 12 → 45 ± 8	9.4 ± 1.0 → 8.7 ± 0.9
20	49 ± 20 → 38 ± 12	9.8 ± 1.8 → 7.6 ± 1.2^b
30	58 ± 15 → 17 ± 4^b	9.4 ± 1.6 → 5.9 ± 1.0^b
40	49 ± 15 → 0 ± 0^b	9.5 ± 0.4 → ^{b,c}

[a] Mean ± SD.
[b] $P < 0.05$.
[c] Could not be determined; block was complete.

Table 3. Changes in the Compound Action Potential Amplitudes and Conduction Velocities of C Fibers Exposed to Different Concentrations of PEG in Sheathed-Nerve Preparations

PEG concentration (%)	Amplitude (mV) changes^a	Conduction velocity (m/sec) changes^a
0	28 ± 15 → 37 ± 22	1.3 ± 0.2 → 1.2 ± 0.2
3	22 ± 8 → 25 ± 10	1.4 ± 0.04 → 1.3 ± 0.1
10	23 ± 14 → 25 ± 14	1.3 ± 0.1 → 1.2 ± 0.1
20	20 ± 6 → 18 ± 6	1.4 ± 0.1 → 1.2 ± 0.05^b
30	24 ± 9 → 7 ± 3^b	1.3 ± 0.1 → 1.0 ± 0.1^b
40	18 ± 3 → 0 ± 0^b	1.4 ± 0.1 → ^{b,c}

[a] Mean ± SD.
[b] $P < 0.05$.
[c] CV could not be determined; block was complete.

3% and 10% PEG did not depress the mean amplitudes of the A, B, and C fibers (Tables 1–3). The slowing of the conduction velocities after 3% and 10% PEG was not significant ($P > 0.05$).

Twenty percent PEG decreased the mean amplitudes of the A, B, and C fiber groups by 9%, 21%, and 8%, respectively (Tables 1–3). Conduction velocities of the A, B, and C fibers decreased by 13%, 22%, and 16%, respectively. The changes in amplitudes were not statistically significant but the decreases in conduction velocities were ($P < 0.05$).

Thirty percent PEG diminished the mean amplitudes of the A, B, and C fiber groups by 24%, 71%, and 71%, respectively (Tables 1–3). The respective conduction velocities decreased by 27%, 36%, and 27%. These changes were significant ($P < 0.05$).

Forty percent PEG abolished the CAPs of the A, B, and C fiber groups. The time to complete block was 40–55 (49 ± 5.5) min for the A fibers, 35–50 (44 ± 5.5) min for the B fibers, and 35–50 (43 ± 5.7) min for the C fibers. These changes were significant ($P < 0.05$).

After washout of the PEG, the CAP amplitudes recovered to at least 80% of baseline values. All recovered within the 2 hr washout time, except in one experiment in which the B fibers took 3.5 hr to attain 80% recovery after exposure to 40% PEG. The time to 80% recovery after washout of the 40% PEG was 25–65 (36 ± 17) min for the A fibers, 35–210 (84 ± 71) min for the B fibers, and 20–100 (48 ± 36) min for the C fibers. Conduction velocities also improved (increased) after washout of the 20–40% PEG. There was no improvement of the conduction velocities following washout of the 3% PEG but there were conduction velocity increases in some of the A (one of five experiments), B (three of five experiments), and C (four of five experiments) nerve fiber preparations after washout of the 10% PEG.

There was no depression of the amplitude or significant slowing of the conduction velocities of the A, B, and C fibers when the pH of the Liley solution was lowered to 6.45. Exposure of the sheathed nerve to 20%, 30%, and 40% PEG at pH 7.4 resulted in the same degree of amplitude depression and conduction velocity slowing as at the lower pH (Table 4).

In the desheathed experiments, the mean amplitudes of the A, B, and C fibers after exposure to 3% PEG were not statistically different ($P > 0.05$) from their baseline mean amplitudes (Table 5). Moreover, there was no difference in action potential amplitudes between treatment and control fiber groups. There also was no significant difference ($P > 0.05$) in the conduction velocity values between the control and PEG groups (Table 6).

The degrees of block (Table 5) by the 20–40% PEG on desheathed nerves were the same as in the sheathed-nerve preparations (Tables 1–3). The time to 100% block after exposure to 40% PEG (A = 55 min, B and C = 50 min) were within the range of values found in the sheathed-nerve experiments. The CAPs of the desheathed nerves also recovered to at least 80% of their baseline values.

Discussion

Glycols are alcohols with two hydroxyl groups in the molecule. Polyethylene glycols (PEGs) are polymeric compounds represented by a large number of ether linkages and terminal hydroxyl groups (12). PEGs are prepared either by the polymerization of ethylene oxide or the dehydration of ethylene glycol (13). The degree of polymerization can be controlled in their preparation. This results in products of different consistencies, from liquids to solid materials (12), with molecular weights from 150 to 10,000 (13). At room temperatures, substances with molecular weights up

Table 4. Changes in the Compound Action Potential Amplitudes and Conduction Velocities after PEG, pH 7.4, in Sheathed-Nerve Preparations

	Nerve fiber					
	A		B		C	
PEG concentration (%)	Amplitude (mV)	CV (m/sec)	Amplitude (mV)	CV (m/sec)	Amplitude (mV)	CV (m/sec)
20	91 → 80	42 → 38	61 → 39	10 → 9	18 → 18	1.4 → 1.2
30	59 → 47	42 → 28	37 → 7	10 → 6	12 → 4	1.4 → 1.1
40	73 → 0	45 → —[a]	13 → 0	8 → —[a]	9 → 0	1.3 → —[a]

Note: One experiment per PEG concentration.
[a]Could not be determined; CAP was completely blocked.

to 600 are liquids whereas those with molecular weights above 1000 are solids (13). PEGs are heat stable and chemically inert. Their low systemic toxicity, wide range of drug compatibilities, and exceptional solubilization characteristics make them useful as vehicles for drugs (14). Examples of drugs with PEG as a vehicle include sodium pentobarbital, parenteral digoxin, methylprednisolone acetate, and triamcinolone diacetate.

In 1952, a long-acting local anesthetic, Efocaine, was introduced that consisted of 5% butyl-p-aminobenzoate, 1% procaine, and 0.2% procaine hydrochloride. These slowly absorbed crystalline substances were dissolved in a vehicle containing 78% propylene glycol and 2% PEG 300 (the number refers to the mean molecular weight). Although Efocaine had a prolonged duration of action, neurological complications were soon reported. These included post-injection neuritis, transverse myelitis, and partial Brown-Sequard syndrome (15). A subsequent study showed that the complications were probably due to the glycol vehicle. The perineural injection of 80% propylene glycol in rabbits caused destructive lesions in the nerve, ranging from axonal and myelin disintegration to severe disorganization of the nerve funiculus (8). In the same study, the intramuscular injection of 10–70% propylene glycol resulted in coagulation necrosis of the muscle.

Intrathecal steroid injections have been used in management of lumbar radiculopathies, adhesive arachnoiditis, and multiple sclerosis (2,4,6). Neurological complications have been reported, however, that include paraplegia, transient bladder paralysis, aseptic meningitis, and adhesive arachnoiditis (3–5). It should be noted that the neural complications (paraplegia, bladder paralysis for 3 weeks) after intrathecal steroid injections occurred in patients with multiple sclerosis. The patients who developed the complications had one to four injections (3–5). Three patients who developed paraplegia were paraparetic before the steroid injections; one patient remained paraplegic and the other two improved after 1 and 4 months (3). It is not possible in these cases to separate the role of the disease from that of injections (16).

The occurrence of neurologic complications after intrathecal steroid injections has been ascribed to PEG (6,7). The basis for this was a report (8) that 80% propylene glycol is neurotoxic. Commercial steroid preparations, however, contain 2.9–3% PEG. The assumption that the neurologic complications were caused by PEG was based on a study (9) that showed axonal degeneration and myelin destruction of rat sciatic nerves after the perineural injection of the suspending vehicle (3% PEG, 9 mg sodium chloride, and 0.2 mg myristyl-gamma-picolinium chloride) of methylprednisolone acetate. However, this study (9) did not evaluate the effects of either PEG or myristyl-gamma-picolinium chloride alone. In addition, in another study, histological examination of the spinal nerve roots and meninges of cats after the epidural injection of the suspending vehicle (3% PEG, 0.2% polysorbate 80, 0.9% benzyl alcohol, and 0.85% sodium chloride) of triamcinolone diacetate showed no effect (17). In contrast to these two studies (9,17), where the suspending vehicle of the steroid preparation was injected, we examined the neural effects of PEG alone.

Different methods have been used to test possible neurotoxicity of drugs. In addition to persistent neurologic blockade after spinal anesthesia in experimental animals (18,19), histopathologic (18–20) and neurophysiologic (20–22) techniques have also been employed. In neurophysiologic studies, several investigators (20–22) looked at the depression or abolition of the CAP amplitude as a measure of neurotoxicity. The duration of drug exposure ranged from 15 min (21,22) to 1 hr (20). A study (21) that investigated the neurotoxicity of 0.2% sodium bisulfite at a pH of 3.0 showed complete and irreversible block of the CAP amplitude of the sheathed rabbit vagus nerve after a 15-min exposure to this antioxidant. Therefore, a 1-hr exposure to PEG should be more than adequate

Table 5. Changes in Compound Action Potential Amplitudes (mV) after PEG in Desheathed Nerves[a]

	Nerve fiber		
PEG concentration (%)	A	B	C
0[b]	102 ± 22 → 100 ± 15	60 ± 13 → 69 ± 14	51 ± 10 → 57 ± 14
3[b]	102 ± 11 → 109 ± 20	67 ± 16 → 70 ± 13	58 ± 11 → 62 ± 14
20	115 → 109	73 → 55	57 → 53
30	116 → 92	66 → 8	44 → 8
40	122 → 0	64 → 0	81 → 0

Note: Five nerves were tested in the 0 and 3% PEG; one nerve was tested in the 20%, 30%, and 40% PEG.

[a] See Tables 1–3 for results on sheathed nerves.

[b] Mean ± SD.

Table 6. Changes in Compound Action Potential Conduction Velocities (M/S) in Desheathed Nerves[a]

	Nerve fiber		
PEG concentration (%)	A	B	C
0[b]	28.2 ± 2.1 → 26.7 ± 2.1	7.7 ± 0.4 → 7.4 ± 0.4	1.1 ± 0.04 → 1.1 ± 0.04
3[b]	29.1 ± 5.1 → 27.2 ± 4.7	9.2 ± 13 → 8.6 ± 0.9	1.2 ± 0.04 → 1.1 ± 0.05
20	36 → 29	11 → 9	1.3 → 1.2
30	29 → 19	9 → 6	1.1 → 0.8
40	38 → [c]	10 → [c]	1.4 → [c]

Note: Five nerves were tested in the 0–3% PEG; one nerve was tested in the 20%, 30%, and 40% PEG.

[a] See Tables 1–3 for results on sheathed nerves.

[b] Mean ± SD.

[c] Could not be determined; CAP was completely blocked.

to demonstrate possible drug-induced neurotoxicity. We also studied changes in conduction velocity since we noted slowing of the conduction velocity before or simultaneously with the depression of the amplitude in experiments involving local anesthetics.

Our study showed the absence of an effect of 3% PEG on transmission of nerve impulses. Although 10% PEG did not decrease the amplitudes or significantly prolong the latencies of the nerve CAPs, this concentration may be considered a sub-blocking concentration since in some of the A, B, and C fibers, conduction velocities improved with washout of the PEG. Twenty percent PEG mildly blocked the CAPs, 30% moderately blocked the CAPs, and 40% completely blocked the nerve CAPs. These effects were reversible with washout of the PEG. The reversibility of PEG effect was surprising since PEG had been thought to be neurolytic (6–8).

Based on the findings of Wood et al. (9), Bromage (7) recommended dilution of the steroid when used for epidural injection to decrease the concentration of the PEG to 0.3%. Because our study showed that 3% PEG has no deleterious effect on nerve transmission, dilution may not be necessary. Dilution of the steroid is still recommended for better spread of the drug since several nerve roots are usually inflamed in disc herniations (1).

The ability of the more concentrated PEG solutions to block impulse conduction may be related to their increased osmotic pressure. Since the osmotic pressure of a solution is directly proportional to the concentration of the solute (23), 20–40% PEG can be considered hyperosmotic or hypertonic. This increased osmolality was accompanied by the increased viscosity of the PEG solution when the higher (20–40%) concentrations were prepared. The increased viscosity is attributable to hydrogen bonding associated with the OH groups in the PEG molecule (24).

Permeant molecules that distribute into all cellular compartments (as PEG probably does) cause no net shift of H_2O at equilibrium, although there may be some transient movement before diffusion of PEG into the nerve. Impairment of impulse conduction with PEG is probably related to the movement of water and ions between the hypertonic solution and the nerve axon and myelin. Axons are highly hydrated, containing 75% (25) to 90% (26) water by weight. In the presence of a hypertonic solution, water passes from the nerve axon to the solution, leading to shrinkage of nerve fibers. On the other hand, the water content of myelin is 40–50% (25). The lyophilic molecules and ions in the hypertonic solution, together with its bound water, penetrate the myelin and increase its volume (26). These structural changes in the nerve axon and myelin may reduce the ion permeability of the axonal membrane or compress the extra-axonal space, thereby elevating the external K^+ concentration and depolarizing the nerve membrane, rendering it refractory to nerve impulse conduction (25).

The decrease in pH with the addition of the PEG may be due to binding or dilution of the buffer used in our Liley solution. Several studies have investigated the effect of pH on nerve impulses. The studies showed that pH over a range of 6.5–9 did not affect the CAP amplitudes (27,28) or the relative amplitudes of sodium conductance (29). The method by which the desired pH value was achieved made a difference; chemical means did not alter baseline parameters (28,29) whereas the use of CO_2 as a buffer increased the block (28,30). The additional block by the CO_2-buffered solutions may be due to a direct depressant effect of CO_2 on nerve excitability (28). The fact that we did not use CO_2 to attain the desired pH of our Liley solution probably explains our findings, that is, the degrees of blockade were the same at pH's 6.5 and 7.4.

The degrees of block by the 20–40% PEG and the time to reach 100% block of the nerve CAPs by the 40% PEG were the same in the sheathed- and desheathed-nerve experiments. This indicates that PEG, with its high molecular weight, passes through the nerve sheath easily. The perineurium, with its inner continuous layer of squamous epithelium, acts as a diffusion barrier to the passage of substances (31). The ability of substances to pass through cellular barriers is independent of their molecular weight (32). Electrolyte solutions penetrate with difficulty, but acetone and alcohol penetrate the nerve sheath readily (32). The PEGs, being dihydric alcohols (33), could therefore pass through the sheath easily.

Adhesive arachnoiditis is another possible complication of intrathecal steroid injections (3,34). We cannot completely exonerate PEG as the cause of arachnoiditis since microscopic examination was not performed in our study. As previously stated, the histologic features of the meninges were the same whether the suspending vehicle of triamcinolone diacetate was or was not injected epidurally (17). However, the intrathecal injection of a nonionic detergent (alkylated phenol ethylene oxide condensate, 1%) causes cellular proliferation in the pia and arachnoid matters in monkeys (35). It should be noted that the four patients who developed arachnoiditis received five, seven, 16, and 23 intrathecal injections, respectively (3,34). Since almost any substance, including isotonic sodium chloride solution (36), causes pleocytosis when injected intrathecally, and since repeated intrathecal injections cause increasing and prolonged cellular reaction (37), numerous intrathecal steroid injections may ultimately result in arachnoiditis.

We conclude that 3% PEG, the concentration used clinically, does not affect nerve conduction. Higher (20–30%) concentrations cause mild to moderate depression of the CAP amplitudes and marked slowing of the conduction velocities. Exposure of the nerve to 40% PEG for 1 hr results in a complete block of nerve transmission. The effects of PEG are the same in the sheathed and desheathed nerves and are independent of pH. All changes are reversible.

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Verapamil Pretreatment before Aortic Cross-Clamping in Patients Undergoing Coronary Artery Bypass Graft

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BARAKA A, USTA N, BAROODY M, HAROUN S, DAGHER I, HADDAD R. Verapamil pretreatment before aortic cross-clamping in patients undergoing coronary artery bypass graft. Anesth Analg 1987;66:560–4.

In 12 of 22 patients with coronary artery disease undergoing elective coronary artery bypass graft (CABG), verapamil (0.075 mg/kg body weight) pretreatment was given on initiation of cardiopulmonary bypass (CPB) before aortic cross-clamping (ACC), whereas no verapamil was used in 10 control patients. The volume of cardioplegia solution required to achieve and maintain cardiac asystole during ACC while on CPB was not significantly different in the two groups. After the release of ACC, the energy of direct current countershock required for defibrillation, the incidence of heart block, and the need for pacemaker were not significantly different. However, defibrillation was more readily achieved by a single countershock in the verapamil group than in the control group. Also, the incidence of ST segment changes after defibrillation was significantly lower in the verapamil group, suggesting that verapamil pretreatment before ACC may potentiate the myocardial preservation achieved by the cardioplegia, and hence may decrease the incidence of ischemic changes during the critical reperfusion period.

Key Words: MYOCARDIAL PRESERVATION, CARDIOPLEGIA—calcium channel blockers, verapamil. MYOCARDIAL ISCHEMIA—ventricular fibrillation, heart block, pacemakers. CARDIOPULMONARY BYPASS—coronary artery bypass graft.

Aortic cross-clamping (ACC) is widely used in patients undergoing coronary artery bypass graft (CABG). To minimize myocardial ischemia after ACC, hyperkalemic hypothermic cardioplegic solutions have been widely used to provide myocardial preservation. Both animal and human studies have shown that the preischemic administration of slow channel calcium blockers helps to preserve myocardial performance and mitochondrial function (1,2). Animal studies show that the addition of verapamil to the cardioplegic solutions improves overall cardiac performance (3). However, in humans, the addition of verapamil to the cardioplegic solution is associated with an increase in need for pacing and inotropic support after ACC release. In contrast, when verapamil is infused before ACC on initiation of cardiopulmonary bypass (CPB), the need for pacing and inotropic support is decreased (4). In our report, verapamil pretreatment was initiated with CPB before ACC. After the release of ACC, the ease of defibrillation, electrocardiogram (ECG) pattern, need for pacing, and the hemodynamic parameters were monitored and compared with those of a control group having no verapamil pretreatment.

Methods

The study included 22 patients with coronary artery disease undergoing elective CABG procedures. The investigation was approved by the Human Studies Committee, and an informed consent was obtained from each patient. Ten patients served as a control group, and 12 patients as the verapamil study group. The two groups were comparable ($P > 0.05$) with respect to age, sex, preoperative ECG findings, number of coronary arteries for grafting, and left ventricular function (Table 1).

All preoperative cardiac medications (Table 2) were continued in both groups until the morning of the operative day. Patients were premedicated 1 hr before induction of anesthesia with intramuscular morphine 10 mg, scopolamine 0.3 mg, and promethazine 25 mg. Hemodynamic monitoring included radial artery cannulation and thermodilution pulmonary artery cath-

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Table 1. Preoperative Data

	Control group (n = 10)	Verapamil group (n = 12)
Age (yr)	54.3	53.3
Sex		
M	9	10
F	1	2
Number of CABGs	2.8 ± 1.1	2.8 ± 0.7
ECG		
MI	5	4
Ischemia	3	6
Normal	2	2
Left ventricular function		
good (EF 0.6)	5	7
fair/bad (EF 0.6)	5	5

Abbreviations: CABG, coronary artery bypass graft; EF, ejection fraction; MI, myocardial infarction.

Table 2. Preoperative Medication

	No. patients	Control dose (mg/day)	No. patients	Verapamil dose (mg/day)
Nifedipine	8	67.5 ± 43.7	12	60 ± 27.9
Isosorbid dinitrate	9	67.8 ± 29.5	12	80 ± 34.6
Propranolol hydrochloride	7	74.4 ± 37.1	9	55.5 ± 26.5
Digoxin	1	0.25	2	0.25

Table 3. ECG Pattern before Cardiopulmonary Bypass

	Control group (n = 10)	Verapamil grou (n = 12)
Normal	6	9
Ischemic changes	2	2
Heart block	2	1

eterization. The calibrated electrocardiogram (ECG) lead V_5 was also monitored (1 mV = 10 mm). Hemodynamic data measured included blood pressure (BP) (mean, systolic, and diastolic), pulmonary artery pressure (PAP) (mean, systolic, and diastolic), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated.

Anesthesia was induced with diazepam 0.2 mg/kg, fentanyl 20 μg/kg, and a mixture of pancuronium 0.05–0.1 mg/kg and alcuronium 0.125–0.25 mg/kg. After laryngoscopy and orotracheal intubation, anesthesia was supplemented with morphine 0.3–0.5 mg/kg. Patients were ventilated with 100% oxygen without additional inhalation anesthetics throughout the procedure. After stabilization of anesthesia and before aortic cannulation, cardiovascular data were recorded.

The patients were randomly divided into two groups. In one group, verapamil 0.075 mg/kg was added to the priming solution of the pump oxygenator, whereas in the control group no verapamil wa used. Cardiopulmonary bypass was initiated using flow of 2.3 $L\cdot m^{-2}\cdot min^{-1}$. Flow and temperature of th perfusate were adjusted to maintain perfusion pressure at 50–80 mm Hg and rectal temperature at 28°C After ACC, cardioplegic solution (K^+ 30 mEq/L at 4°C was infused in the aortic root. The volume of cardioplegic solution needed to achieve and maintain ca diac asystole as monitored by the ECG was calculate in the two groups.

After removal of the ACC, ventricular fibrillatio (VF) was treated with a Hewlett-Packard defibrillato the number of countershock trials and the energy required were recorded. Also, the ECG was monitore (V_5) for detection of arrhythmias, changes in ST segments or T waves, and/or development of heart block Whenever second or third degree blocks were diagnosed, ventricular pacing was initiated, and the ou put threshold required for pacing was recorded. Afte rewarming the patient to a rectal temperature of 35° and assuring the presence of normal levels of arteri blood gas tensions and serum electrolytes, CPB wa discontinued. Nitroglycerine and inotropic suppo were used whenever necessary. One hr after bypas and before transfering the patient to the cardiac su gery intensive care unit (CSU), the hemodynamic dat in the two groups were compared.

Statistical Analysis

The paired Student's *t*-test was used for data expressed as mean ± SD, while the χ^2-analysis was use to compare proportions. $P < 0.05$ was considered statistically significant.

Results

Hemodynamic Data and ECG Pattern before Cardiopulmonary Bypass

ECG pattern (Table 3) and hemodynamic data (Tabl 4) before aortic cannulation were satistically comparable in both the control and the verapamil group ($P > 0.05$).

Table 4. Hemodynamic Data Before Cardiopulmonary Bypass

	Control group	Verapamil group
HR (beats/min)	81.2 ± 13.5	85.7 ± 19.4
Mean BP (mm Hg)	71.8 ± 6.0	68.6 ± 8.2
PCWP (mm Hg)	10.7 ± 3.5	7.9 ± 5.6
CO (L/min)	3.9 ± 0.6	4.4 ± 1.0
SVR (mm Hg·min·L^{-1})	15.3 ± 2.1	14.1 ± 4.2
PVR (mm Hg·min·L^{-1})	1.3 ± 0.2	1.3 ± 0.6

Abbreviations: HR, heart rate; BP, blood pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Cardiopulmonary Bypass

Total CPB time was 75.8 ± 25.3 min in the control group, and 86.9 ± 16.7 min in the study group ($P > 0.05$). SVR during CPB was 9.4 ± 0.5 mm Hg·min·L^{-1} in the control group and 8.7 ± 1.5 mm Hg·min·L^{-1} in the study group ($P > 0.05$). The ACC time was 38.9 ± 14.4 min in the control group, and 44.3 ± 10.0 min in the verapamil group ($P > 0.05$).

Cardioplegia during Aortic Cross-Clamping

Three patients in the control group developed VF after initiation of CPB but before ACC at a temperature of 32.7 ± 1.4°C, whereas six patients developed VF after ACC, and one patient had no VF. In the verapamil group, three patients developed VF before ACC at a temperature of 32.0 ± 1.6°C, seven developed VF after aortic cross-clamping and two did not develop VF. The volume of cardioplegic solution required to achieve cardiac asystole was 383 ± 178.8 ml in the control group and 420 ± 239.4 ml in the study group ($P > 0.05$). The volume of cardioplegia solution required to maintain cardiac asystole throughout the period of ACC was 1385 ± 273.9 ml in the control group and 1383 ± 228.9 ml in the study group ($P > 0.05$).

ECG Pattern after Release of Aortic Cross-Clamping

With termination of ACC in the control group, spontaneous defibrillation occurred in one patient, defibrillation was needed once in four patients, and five patients needed repeated attempts of defibrillation. In one of the latter five patients, recurrent refractory ventricular fibrillation did not respond to repeated doses of lidocaine (2 mg/kg), bretylium (5 mg/kg) or multiple DC countershocks: defibrillation was readily achieved after the IV injection of verapamil 0.075 mg/kg. In the verapamil group, spontaneous defibrillation also occurred in one patient, defibrillation was needed once in seven, and repetitive attempts at defibrillation were needed in only four. The mean countershock output required for defibrillation was 8.2 ± 1.5 J in the control group and 7.8 ± 2.6 J in the study group. The difference between the mean outputs of countershocks required for defibrillation between the two groups was not significant ($P > 0.05$).

Table 5. ECG Pattern Before Defibrillation

	Control group ($n = 10$)	Verapamil group ($n = 12$)
Normal	3	1
Ischemic changes	6	1
First degree block	1	1
Second/third degree block	6	10

In the control group, the ECG showed normal sinus rhythm in three patients, and a first degree heart block in one patient after defibrillation (Table 5). In six patients, a second or third degree heart block was noted, and ventricular pacing was needed; the mean output threshold required for pacing was 4.7 ± 2.6 mA. In the verapamil group, one patient had normal sinus rhythm and one developed first degree block. In 10 patients, a second or third degree block requiring ventricular pacing occurred; the output threshold required for pacing was 4.6 ± 3.0 mA. There was no significant difference between the incidence of pacing and the threshold output required in the two groups ($P > 0.05$). Ischemic changes in ST segments (elevation or depression > 1 mm) occurred in 6 of 10 patients of the control group, and only in 1 of 12 patients of the verapamil group; the difference was statistically significant. In one patient of the control group having a marked ST segment depression, verapamil 0.075 mg/kg was subsequently injected and was followed by rapid restoration of an isoelectric ST segment (Fig. 1).

Hemodynamic Parameters after CPB

One hr after termination of CPB, the ST segment improved and the heart resumed its own rhythm in all patients. Hemodynamic parameters (Table 6) were also comparable in the two groups ($P > 0.05$). Inotropic support and nitroglycerine infusion were necessary in four patients in the control group and in two in the verapamil group ($P > 0.05$).

Discussion

During myocardial ischemia, a defect in Ca^{2+} homeostasis leads to excessive entrance of Ca^{2+} into the intracellular space (5–8). In addition, Ca^{2+} accumu-

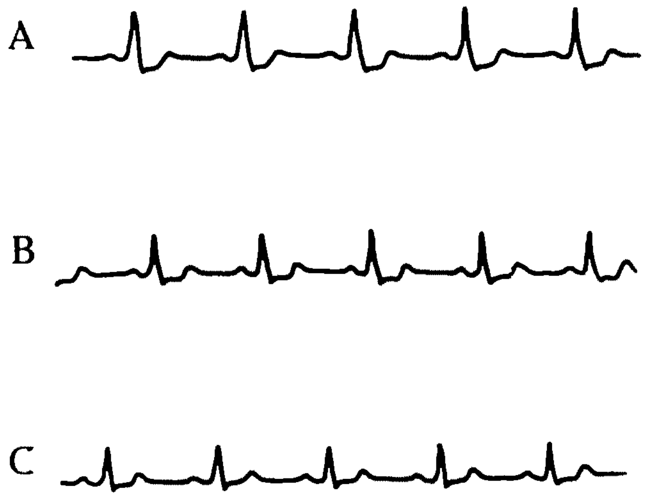

Figure 1. ECG tracings in one of the patients in the control group. (A) ST segment depression after release of ACC and restoration of sinus rhythm. (B) ECG 1 min after injection of verapamil 0.075 mg/kg. (C) ECG 5 min after the injection of verapamil, showing restoration of an isoelectric ST segment.

Table 6. Hemodynamic Data 1 Hr After Cardiopulmonary Bypass

	Control group (n = 10)	Verapamil group (n = 12)
HR (beats/min)	79.9 ± 10.8	81.2 ± 13.9
Mean BP (mm Hg)	74.2 ± 8.5	77.2 ± 15.0
PCWP (mm Hg)	12.2 ± 2.9	13.2 ± 4.8
CO (L/min)	3.8 ± 0.6	3.82 ± 1.0
SVR (mm Hg·min·L^{-1})	16.5 ± 1.9	17.7 ± 6.4
PVR (mm Hg·min·L^{-1})	0.7 ± 0.6	1.1 ± 0.9

Abbreviations same as in Table 4.

lates in the mitochondria and impairs mitochondrial oxidation-phosphorylation, thus decreasing high energy phosphate production (9).

The high intracellular Ca^{2+} concentration activates the actin-myosin ATPase enzymatic system, which in turn causes excessive hydrolysis of ATP (10). The end result is an imbalance between production and utilization of high energy phosphates. Therefore, the initial ischemic insult can result in a vicious circle in which the increase in intracellular calcium plays a major role. Furthermore, reperfusion after ischemia does not always result in rapid and complete recovery of the cardiac function and metabolism, but may even result in further deterioration associated with a further increase in intracellular Ca^{2+} concentration. To avoid the harmful effects of both myocardial ischemia and reperfusion, calcium channel blockers have been used to inhibit the transsarcolemmal Ca^{2+} influx. Verapamil, one of the calcium channel blockers evaluated, reduces the extent of subendocardial infarction after experimental occlusion of the circumflex artery in dogs from 34% without verapamil to 8% of the anatomic area at risk (11). In addition, verapamil can preserve high levels of energy phosphates (12) and decrease the increase in intracellular calcium as a result of ischemia (9). To be effective verapamil has to be given before the onset of ischemia (13,14).

Animal studies involving the addition of verapamil to the cardioplegic solution demonstrate better cardiac performance with verapamil plus cardioplegia than with standard potassium cardioplegia alone (3). In humans, Kaplan et al. (4) demonstrated that the O_2 saturation difference between the radial artery and coronary sinus blood immediately after ACC release was lower in patients receiving verapamil, suggesting an improvement in the oxygen supply-demand relation. However, when verapamil was added to the cardioplegia solution, there was a higher incidence of prolongation of the PR interval and AV block, along with a greater need for pacing and inotropic support, than in another group given verapamil before ACC on initiation of CPB (4).

In our study, verapamil was added to the priming solution of the pump oxygenator to perfuse the myocardium on initiation of CPB and before ACC. The incidence of VF and the volume of cardioplegic solution required to achieve and maintain cardiac asystole after initiation of CPB and applying ACC were not significantly different in the two groups. After the release of ACC, the energy of DC countershock required for defibrillation, the incidence of heart block, and the need for pacemaker also were not significantly different, whether myocardial preservation was achieved by cardioplegia alone or by verapamil pretreatment plus cardioplegia. However, defibrillation was more readily achieved by a single countershock in the verapamil group than in the control group. Also, one patient in the control group developed recurrent refractory ventricular fibrillation that could be defibrillated only after the subsequent injection of verapamil. Previous investigations have shown that verapamil can successfully control intractable ventricular tachycardia, fibrillation, or both, after cardiopulmonary bypass (15–17). The effectiveness of verapamil (a calcium channel blocker) in controlling recurrent reperfusion ventricular arrhythmias suggests that calcium-dependent ionic currents may play an important role in the genesis and perpetuation of life-threatening ventricular arrhythmias in the acutely ischemic myocardium (18).

The incidence of ischemic ST segment changes during the reperfusion period after aortic unclamping was greater in the control group than in the verapamil group. Previous reports have also shown that transient ST segment changes are frequent after reperfusion following aortocoronary bypass grafting, and usually become evident with resumption of supraventricular rhythm after aortic unclamping (19). Although transient, such changes often recur later in the postoperative period and are associated with higher postoperative serum levels of creatine kinase MB, indicating myocardial damage (19). The etiology of the ECG changes is not clear, but the differential diagnosis includes inadequate myocardial protection, or transient occlusion of coronary artery or graft by spasm (20), embolism, or thrombosis (19,20). In our study, the low incidence of the ST changes after aortic unclamping in the verapamil pretreated group suggests either protection against coronary artery and graft spasm, or better myocardial preservation during ACC. Verapamil pretreatment before ACC may potentiate the myocardial preservation achieved by the cardioplegia, and hence may decrease the incidence of ischemic changes during the critical reperfusion period.

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Dopamine Compared with Dobutamine in Experimental Septic Shock:

Relevance to Fluid Administration

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VINCENT J-L, VAN DER LINDEN P, DOMB M, BLECIC S, AZIMI G, BERNARD A. Dopamine compared with dobutamine in experimental septic shock: relevance to fluid administration. Anesth Analg 1987;66:565–71.

The hemodynamic effects of dopamine and dobutamine (at doses of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were compared during fluid resuscitation from septic shock induced by endotoxin (3 mg/kg) in the dog. In the first part of the study, when a standard amount of saline solution was infused (in 24 dogs), dopamine infusion resulted in higher cardiac filling pressures than did dobutamine infusion, whereas dobutamine infusion resulted in higher cardiac output. In the second part of the study, when fluid infusion was titrated to maintain pulmonary artery balloon-occluded pressure at constant level (in 24 dogs), the total amount of fluids was significantly greater with dobutamine than when dopamine was used (109 ± 13 vs 71 ± 10 ml/kg). The combination of dobutamine with fluids resulted in significantly greater stroke volume (39.6 ± 3.8 vs 21.0 ± 4.0 ml, $P < 0.05$) and oxygen consumption (194 ± 18 vs 144 ± 8 ml/min, $P < 0.05$). The different effects of dopamine and dobutamine on cardiac filling pressures can be due to differences in effects on myocardial contractility, ventricular afterload, and cardiac compliance. This experimental study indicates that when fluid therapy is combined with adrenergic agents in resuscitation from septic shock, dobutamine can be associated with higher cardiac output and oxygen transport and can result in higher tissue oxygen consumption than dopamine.

Key Words: SHOCK—septic. SYMPATHETIC NERVOUS SYSTEM—dopamine, dobutamine.

Septic shock is characterized by a distributive defect associated with peripheral pooling of blood and decreased venous return to the heart (1,2). In addition, myocardial depression can occur relatively early in relation to decreased coronary perfusion, myocardial edema, or release of toxic factors (1–4). Besides the removal of the septic focus and the administration of antibiotic agents, immediate therapy of septic shock focuses on restoration of hemodynamic stability by the administration of intravenous fluids and adrenergic agents. Dopamine is probably the most popular agent for its combined α, β, and dopaminergic properties, resulting in combined increases in arterial pressure, cardiac output, and selective increase in renal blood flow. Dobutamine, another sympathomimetic agent with strong inotropic action but little effect on the peripheral vasculature, is also used in the treatment of septic shock, especially when a low flow stat is associated with myocardial depression (2).

An important issue in the choice between dopamine and dobutamine is their relative effects on cardiac filling pressures and therefore their possible interference with concurrent fluid infusion. Variou studies in patients suffering from cardiogenic shoc or severe congestive heart failure or recovering fror cardiac surgery have indicated that dopamine increases cardiac filling pressures more than dobutamine (5–12). In addition, a recent study (13) indicate that dopamine also can increase cardiac filling pressures in acutely ill patients with respiratory failure.

In septic shock, Regnier et al. (14) also observe higher cardiac filling pressures with dopamine tha with dobutamine infusion. However, comparative trial of drugs in patients with septic shock are preclude by the typically unstable conditions. We therefor compared the use of dopamine and dobutamine together with fluid infusion after endotoxin administration in the dog. Because drug administration t achieve a given response is difficult in these unstable conditions, we administered fixed doses o 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of both adrenergic agents.

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We first studied the effects on filling pressures of dopamine or dobutamine administered with a standard fluid regimen infused by formula. The hypothesis being tested was that filling pressures would be higher with dopamine infusion. In the second part of the study, we infused amounts of intravenous fluids necessary to maintain filling pressures at constant levels as commonly done clinically. The tested hypothesis was then that dobutamine administration would be associated with the use of larger volumes of intravenous fluids.

Material and Methods

Our study included 48 large mongrel dogs (29 ± 5 kg) anesthetized with 25 mg/kg of pentobarbital, intubated, and mechanically ventilated on control mode with air (Spiromat II-M 5000, Dräger, Lubeck, FRG). Respiratory rate was set at 12 breaths/min, and tidal volume was adapted to maintain Pa_{CO_2} between 35 and 40 mm Hg. Supplemental doses of 25–50 mg pentobarbital were added as necessary to maintain anesthesia.

Electrodes were attached to the four limbs for heart rate (HR) monitoring. A Swan-Ganz catheter (model 93A-131-7F, Edwards Laboratories, Santa Ana, CA) was inserted via a jugular vein into a pulmonary artery for measurement of pulmonary artery pressure (PAP), pulmonary artery balloon-occluded pressure (PAOP), and right atrial pressure (RAP). Two other catheters (16G8, Becton, Dickinson and Co., Rutherford, NJ) were inserted, one from a femoral artery into distal aorta for arterial pressure (AP) measurement and blood withdrawal, and one into a femoral vein for saline and drug infusion.

After the initial hemodynamic and gasometric evaluation, 3 mg/kg of *Escherichia coli* endotoxin (055B5, Difco Laboratories, Detroit, MI) was injected in 5 min. The dog was observed for 30 min before fluid resuscitation with 0.9% saline was started.

A first 30-min period of rapid fluid repletion (period A) was followed by a 3-hr saline infusion (period B). Intravenous fluids were administered according to two successive protocols: 1) By formula (24 dogs). Saline solution was infused at a rate of 20 $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$ for the first 30 min (period A) and 10 $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$ thereafter (period B). During period B, dogs were randomized into three groups treated with saline solution alone (eight control dogs) or saline combined with dopamine (eight DOP-treated dogs) or dobutamine (eight DOB-treated dogs) at a constant rate of 6 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$. 2) According to PAOP (24 dogs). Saline infusion was given (in $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$) every 10 min in amounts needed to restore (period A) and

Table 1. Hemodynamic Data Obtained in the Three Groups of Dogs When Intravenous Fluids Were Administered by Formula

	Control (n = 8)			Dopamine (n = 8)			Dobutamine (n = 8)		
	Base	+ 60 min	+ 240 min	Base	+ 60 min	+ 240 min	Base	+ 60 min	+ 240 min
Mean arterial pressure (mm Hg)	124.8 ± 5.4	83.4 ± 8.3	85.3 ± 14.3	136.0 ± 6.3	92.0 ± 7.8	113.3 ± 9.5	136.8 ± 3.9	81.1 ± 6.2	102.3 ± 10.8
Pulm arterial pressure (mm Hg)	14.9 ± 1.0	13.6 ± 1.0	13.5 ± 1.0	16.1 ± 1.2	14.0 ± 1.3	16.1 ± 1.6[a]	14.3 ± 0.9	10.5 ± 1.5	12.3 ± 1.2[a]
PAOP (mm Hg)	5.6 ± 0.8	4.9 ± 0.9	5.0 ± 0.8	5.8 ± 0.5	5.5 ± 0.8	6.3 ± 0.5[a]	5.0 ± 0.8	3.4 ± 0.9	4.1 ± 0.9[a]
Right atrial pressure (mm Hg)	4.4 ± 0.9	4.4 ± 1.1	4.9 ± 0.8	5.4 ± 0.7	4.5 ± 0.7	5.9 ± 1.0	4.5 ± 0.8	2.4 ± 0.7	3.5 ± 1.2
Heart rate (beats/min)	152 ± 10	153 ± 8	147 ± 12	155 ± 9	152 ± 7	153 ± 8	150 ± 8	153 ± 10	178 ± 10
Cardiac output (L/min)	4.04 ± 0.45	3.75 ± 0.42	3.14 ± 0.37	4.19 ± 0.24	3.36 ± 0.49	3.60 ± 0.54	3.41 ± 0.48	2.59 ± 0.54	4.03 ± 0.47
Stroke volume (ml)	27.2 ± 3.1	24.4 ± 2.1	22.0 ± 2.4	27.7 ± 2.1	22.0 ± 3.0	24.9 ± 3.5	23.5 ± 3.7	17.2 ± 3.1	22.8 ± 2.5
LVSW (g·m)	43.7 ± 5.2	26.2 ± 4.4	24.2 ± 5.5	49.5 ± 5.2	27.7 ± 5.2	36.0 ± 6.6	42.1 ± 6.9	18.2 ± 3.3	30.6 ± 2.9
SVR ($dynes{\cdot}sec{\cdot}cm^{-5}$)	2664 ± 406	1781 ± 245	2173 ± 409	2519 ± 145	2347 ± 301	2540 ± 311	3099 ± 523	2428 ± 516	1959 ± 256
O_2 delivery (mL/min)	663 ± 65	669 ± 86	571 ± 29	739 ± 24	667 ± 89	759 ± 98	623 ± 75	518 ± 92	915 ± 96
$\dot{V}O_2$(ml/min)	154.2 ± 16.6	183.6 ± 13.4	157.0 ± 15.7	149.9 ± 15.5	158.1 ± 11.7	136.0 ± 18.0	192.0 ± 34.0	170.7 ± 32.4	175.1 ± 16.4

[a] $P < 0.05$ DOP vs DOB.

Abbreviations: PAOP, pulmonary artery balloon-occluded pressure; LVSW, left ventricular stroke work; SVR, systemic vascular resistance; $\dot{V}O_2$, oxygen consumption.

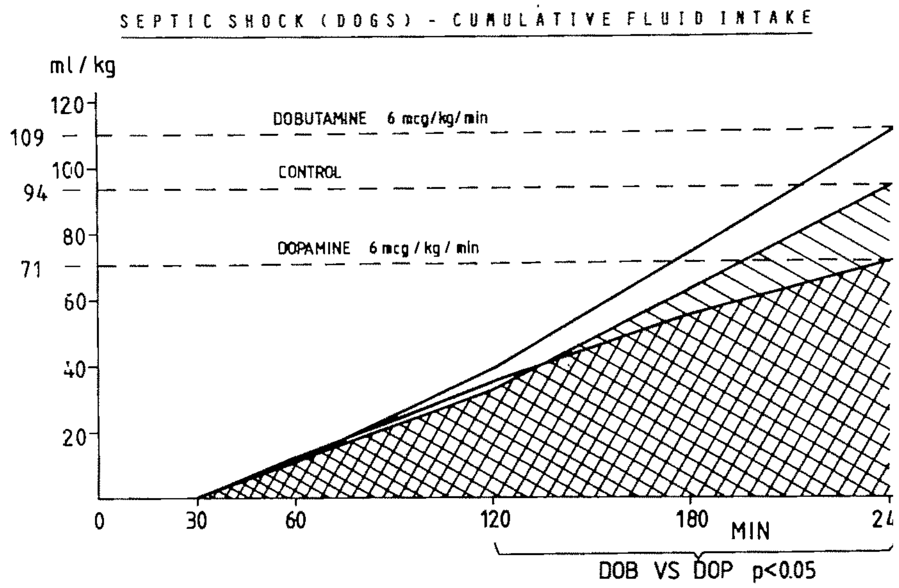

Figure 1. Cumulative fluid intake in the three groups of dogs. For the last 2 hr, the total amount of fluids infused was significantly greater in DOB-treated than in DOP-treated dogs.

maintain (period B) PAOP at baseline levels. During period B, dogs were randomized into three groups treated as in the first protocol with saline solution alone (eight control dogs) or saline combined with dopamine (eight DOP-treated dogs) or dobutamine (eight DOB-treated dogs) at a constant rate of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

At the end of the 4-hr experiment, treatment was discontinued and catheters were removed. The dogs were extubated and returned to their cage until the next morning.

Heart rate, AP, and PAP were continuously recorded (model 7404, Hewlett-Packard, Palo Alto, CA); the zero pressure level was set at the midchest level of the animal. Intravascular pressures were measured at end-expiration from the paper trace. Cardiac output (CO) was measured by the thermodilution technique (computer 9520A, Edwards Laboratories) by repeated injections of 5 ml of iced (<3°C) 5% dextrose in water at end-expiration. Three to five measurements were averaged for each CO determination. Pressures, CO, and HR were determined before the endotoxin injection and every 30 min thereafter. Arterial and mixed venous blood samples were withdrawn at baseline and after 30, 60, 120, 180, and 240 min for measurements of blood gas tensions (ABL 2, Radiometer, Copenhagen, Denmark). Hemoglobin saturation (So_2) was calculated by the Rossing and Cain's nomogram (15). Lactate concentrations were measured enzymatically by an automated system (ACA, Du Pont Instruments, Wilmington, DE).

Stroke volume (SV), left ventricular stroke work (LVSW), systemic vascular resistance (SVR), oxygen delivery, and oxygen consumption ($\dot{V}o_2$) were ca culated by the following formulas:

$$SV\ (ml) = CO / HR$$

$$LVSW\ (g \cdot m) = SV \times (AP - PAOP) \times 0.0136$$

$$SVR\ (dynes \cdot sec \cdot cm^{-5}) = (AP - RAP) \times 79.9 / CC$$

$$O_2\ delivery\ (ml/min) = CO \times Cao_2 \times 10$$

$$\dot{V}o_2\ (ml/min) = CO \times (Cao_2 - Cvo_2) \times 10,$$

where Cao_2 and Cv_{O_2} represent the oxygen content of the arterial blood and the mixed venous blooc respectively.

Statistical evaluation was performed by two-wa analysis of variance and Student's t-test, using th Bonferroni adjustment. The level of statistical signi icance was set at $P < 0.05$. All values are given a mean ± SEM.

Results

Fluid Infusion by Formula

Arterial pressure rapidly decreased after endotoxi administration and remained low in control dogs (Ta ble 1). DOP- and DOB-treated dogs had somewha higher arterial pressure and LVSW, and significantl higher O_2 delivery ($P < 0.05$) than did control dogs During period B, CO declined in control dogs ($P <$ 0.05), increased slightly in DOP-treated dogs ($P =$ NS), and increased significantly in DOB-treated dog ($P < 0.05$). The only significant differences betwee DOP- and DOB-treated dogs were higher levels c

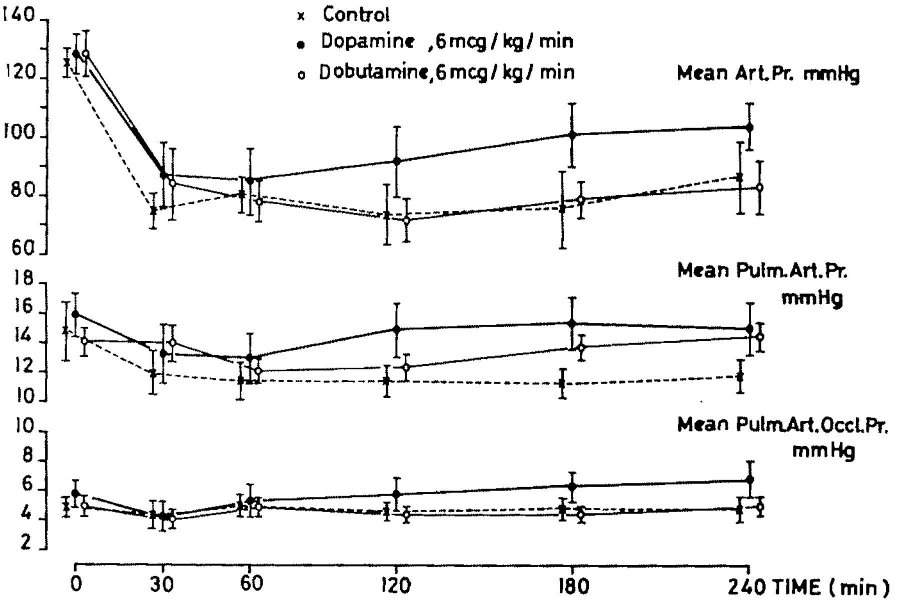

Figure 2. Arterial pressure, mean pulmonary artery pressure, and pulmonary artery balloon-occluded pressure in the three groups of dogs.

PAP and PAOP in DOP-treated dogs at the end of the experiment.

Five DOP-treated, four DOB-treated, and two control dogs survived until the next morning (differences not significant).

Pulmonary Artery Balloon-Occluded Pressure

When fluid was infused in volumes adequate to restore PAOP to baseline levels, the total amount of fluids administered was greatest in the DOB-treated dogs. Cumulative fluid intake was 109 ± 13 ml/kg in DOB-treated dogs, 94 ± 11 ml/kg in control dogs, and 71 ± 10 ml/kg in DOP-treated dogs. Differences in fluid intake between DOP- and DOB-treated dogs were statistically significant for the last 2 hr of the experiment (Fig. 1). Although arterial pressure was slightly higher in DOP-treated dogs, differences in intravascular pressures did not reach statistical significance (Fig. 2). Heart rate, CO and $\dot{V}O_2$ were greater in DOP and DOB than in control dogs (Figs. 3 and 4). CO was significantly higher with DOB than with DOP ($P < 0.02$); this was entirely due to a higher SV (39.6 ± 3.8 vs 21.0 ± 4.0 ml, $P < 0.05$) (Fig. 3). SVR was significantly lower in DOB-treated dogs (Fig. 4). In relation with a higher O_2 delivery in DOB- than in DOP-treated dogs (1042 ± 132 vs 719 ± 69 ml/min, P = NS), $\dot{V}O_2$ was significantly higher in DOB-treated dogs (194 ± 18 vs 144 ± 8 ml/min, $P < 0.05$) (Fig. 4). However, there was no difference in lactate concentration, which decreased during treatment from 4.8 ± 0.8 to 3.7 ± 0.7 mEq/L in DOP-treated dogs and from 4.8 ± 0.5 to 3.8 ± 0.6 mEq/L in DOB-treated dogs.

During period B, hematocrit increased in DOP-treated dogs and decreased in the two other groups (Table 2). Protein concentration decreased in all groups; however it decreased to a lesser extent in DOP-treated dogs (Table 2).

Dogs generally developed nonbloody diarrhea. One control dog, one DOP-treated dog, and three DOB-treated dogs survived until the next morning (differences not significant).

Discussion

Our study investigated the utility of dopamine and dobutamine, two largely used adrenergic agents, with fluid administration during septic shock. Fluid therapy is essential in the treatment of septic shock to compensate for extravascular losses, improve tissue perfusion and restore venous return to the heart (2,16). Fluid therapy can be limited by increases in filling pressures that could result in pulmonary edema without further hemodynamic improvement. Vasoactive agents are also often indicated to maintain perfusion pressure and tissue blood flow, but could interfere with fluid therapy.

During dopamine administration, LV filling pressures usually increase together with CO in congestive heart failure (5–7), in cardiogenic shock (8,9), after cardiac surgery (10–12), or in acute respiratory failure (13). Because dobutamine tends to have opposite effects on cardiac pressures (5–12), the combination of

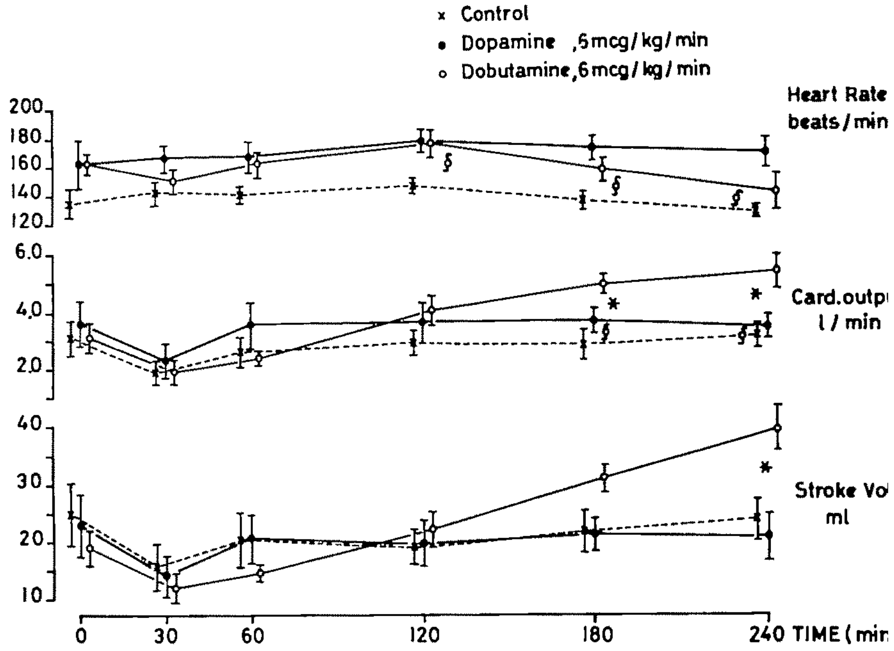

Figure 3. Heart rate, cardiac output, and stroke volume in the three groups of dogs. $^*P < 0.05$ between DOP- and DOB-treated dogs; $§P < 0.05$ between treated and control dogs.

dopamine and dobutamine sometimes has been suggested to cumulate the effects of the two drugs while limiting the increase in LV filling pressures induced by dopamine (9).

The effects of dopamine and dobutamine on cardiac filling pressures in septic shock have been studied less extensively. Regnier et al. (14) compared the administration of variable doses of dopamine and dobutamine in nine patients in septic shock and observed that for comparable increases in cardiac output and LV work, PAOP increased slightly from 11 ± 2 to 12 ± 2 mm Hg (P = NS) with dopamine, but decreased from 12 ± 1 to 7.5 ± 1 ($P < 0.01$) with dobutamine, the difference in values with the two drug regimens being highly significant ($P < 0.01$).

We studied the potential differences between dopamine and dobutamine under controlled experimental conditions in dogs. The model of septic shock induced by endotoxin administration in animals has often been criticized for its generation of a low flow state, whereas hyperdynamic state better characterizes clinical septic shock (17). In our present study, high doses of endotoxin were used to induce a severe shock state associated with significant lactacidemia. Interestingly, CO was maintained when cardiac filling pressures were restored at control level, indicating that decreased venous return plays a major role in the low flow state of endotoxin shock. Because arterial hypotension persisted despite fluid therapy, this represented a low vascular resistance type of shock. Even though myocardial depression has been observed as early as two hr after endotoxin administration (3), th role of myocardial failure was probably limited in thes relatively short-term conditions.

Septic shock is a dynamic process precluding dru titration during the experiment, so that constant dose of dopamine and dobutamine were infused. A moc erate dose of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was chosen because would have significant cardiovascular effects whil avoiding excessive α-mimetic actions of higher dose of dopamine (18). When a standard fluid regimen wa given, the effects on CO were greater with dobut mine than with dopamine. In addition, dopamin tended to increase and dobutamine to decrease ca diac filling pressures, so that the differences in PAO became significant after 3 hr of drug infusion.

Reasons for these differences in cardiac filling pres sures with dopamine and dobutamine infusion ar not clear. They can be related to differences in dia stolic volumes of the cardiac chambers, to changes i ventricular diastolic mechanic properties, or to both Dopamine increases venous return to the heart by α adrenergic mediated venoconstriction, by lowered ve nous resistance to blood flow, or both (19–21). Usin radionuclide techniques, Molloy et al. (13) found tha dopamine significantly increased end-diastolic vo ume in patients with acute respiratory failure. How ever, dobutamine also reduces venous capacitance b a α-adrenergic effect on the vascular smooth muscl (22). Using the thermodilution technique to measur right ventricular volumes, we recently observed i acutely ill patients that even though right atrial pres

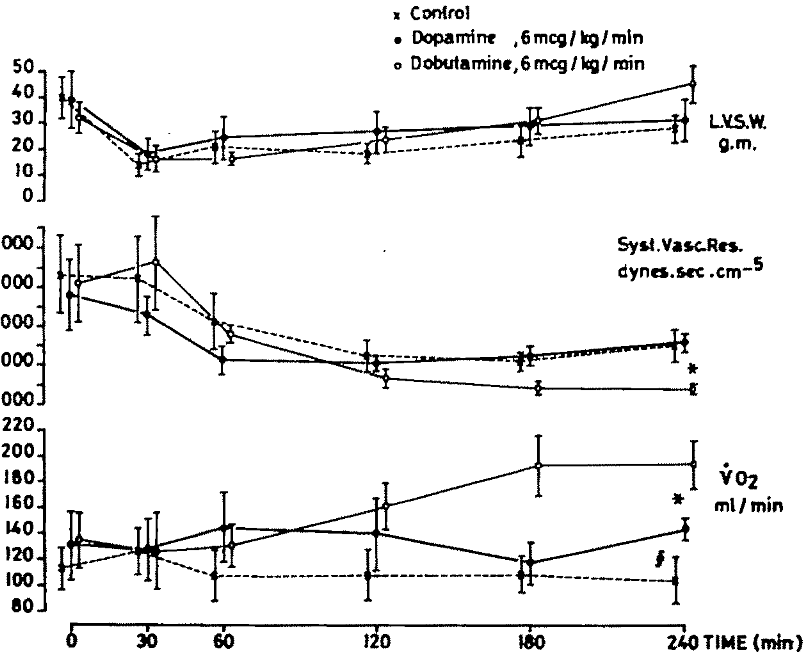

Figure 4. Left ventricular stroke work (LVSW), systemic vascular resistance, and oxygen consumption ($\dot{V}O_2$) in the three groups of dogs. *$P < 0.05$ between DOP- and DOB-treated dogs; §$P < 0.05$ between treated and control dogs.

Table 2. Evolution of Hematocrit and Serum Proteins Concentration in the Three Groups of Dogs.

	Baseline	+ 30 min	+ 60 min	+ 240 min
Hematocrit (%)				
Control	41.7 ± 2.3	48.7 ± 2.7	48.7 ± 2.5	44.3 ± 2.3
Dopamine	42.9 ± 2.5	47.7 ± 2.7	50.6 ± 3.0	50.4 ± 2.3
Dobutamine	40.6 ± 2.8	53.3 ± 3.3	52.3 ± 4.1	50.8 ± 4.0
Proteins (g/dl)				
Control	5.80 ± 0.20	5.56 ± 0.14	5.25 ± 0.11	3.45 ± 0.25
Dopamine	5.58 ± 0.17	5.48 ± 0.21	5.27 ± 0.24	4.51 ± 0.18
Dobutamine	6.40 ± 0.36	5.95 ± 0.35	5.66 ± 0.32	3.65 ± 0.24

sure was higher during dopamine than during dobutamine administration, right ventricular end-diastolic volumes were similar with both drugs (23).

In the second part of our study, fluid infusion was given in volumes adequate to maintain a given level of PAOP, as it is commonly done clinically. In agreement with the results in the first series of experiments, the total amount of fluid infused was significantly greater with dobutamine than with dopamine. The lack of decrease in hematocrit and the slighter decrease in serum protein levels with dopamine administration was consistent with a smaller plasma volume in dopamine-treated animals.

Despite the similarity in PAOP, the combined administration of dobutamine and fluids was associated with a higher stroke volume. Two possibilities can be considered. First, if left ventricular preload was constant, differences in contractility, afterload, or both, should account for the differences in stroke volume. Dobutamine can have stronger positive inotropic (24) and afterload-reducing actions (7). The latter is consistent with the lower systemic vascular resistance measured under dobutamine infusion, although left ventricular afterload was probably low in the present experiments. This first possibility is supported by the greater increase in CO with dobutamine in the first part of the study.

A second possibility is that left ventricular end-diastolic volume was smaller and that cardiac compliance was decreased with dopamine. This could be explained by different effects of dopamine and dobutamine on coronary blood flow, as it has been observed during acute myocardial ischemia (25). Clearly, more than one mechanism could be responsible for the different effects of dopamine and dobutamine on cardiac filling pressures.

The higher cardiac output during dobutamine administration was associated with a higher $\dot{V}O_2$, indicating that nutrient blood flow to the tissues was increased. Another alternative would be that dobutamine but not dopamine directly increased cellular metabolism, but this is unlikely. Because circulatory shock represents insufficient cellular oxygen availability, an increase in oxygen consumption is a salutary sign. Clinical studies have indicated that an increase in $\dot{V}O_2$ in circulatory shock is associated with a better prognosis (16). The lack of difference in lactate concentrations in our study could be due to the short duration of the experiments, a concurrent "washout" effect on lactate, or both.

Although the hemodynamic data appear more favorable in the dobutamine treatment group under the present experimental conditions, we do not imply that dopamine should be replaced by dobutamine in septic shock. First, the use of either dopamine or dobutamine did not significantly increase overall survival. Second, we strongly believe treatment of acute circulatory failure should be tailored according to the hemodynamic conditions. Dopamine could be indicated in severe hypotension, especially when cardiac output is high. The renal effects of low doses of dopamine could also be considered. By its different effects on cardiac filling pressures, dobutamine can facilitate fluid administration and the association of dobutamine with fluids can increase tissue oxygen availability and consumption. Other studies are needed to define the clinical applicability and potential benefit of these observations.

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ANESTH ANALG
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Clinical Reports

Sodium Bicarbonate Attenuates Pain on Skin Infiltration with Lidocaine, with or without Epinephrine

Warren McKay, MD, Richard Morris, MBBS, FFARACS, and Phillip Mushlin, MD, PhD

Anesthetics produce pain on skin infiltration (1,2). The relation of this local anesthetic-induced pain to pH of the local anesthetic solution has, however, not been evaluated. Commercial preparations of local anesthetics are prepared as acidic solutions of the salts to promote solubility and stability. Further increases of acidity in local anesthetic solutions containing epinephrine are avoided by the addition of epinephrine to plain lidocaine (3); sodium bicarbonate can also be used to increase pH. Such increases in pH, by increasing the ratio of nonionized to ionized local anesthetic, alter the pharmacologic properties of local anesthetics. For example, addition of sodium bicarbonate to preparations of local anesthetics increases spread and duration of sensory blockade and lessens the time to onset of anesthesia (4,5). The present double-blind, randomized study was designed to determine the relation between pH of anesthetic solutions and production of pain associated with infracutaneous injection of the local anesthetic, lidocaine.

Methods

This investigation was approved by our hospital's Human Investigations Committee. Twenty-four young, healthy volunteers gave consent and participated in the study. Each subject received an intradermal injection of normal saline solution and the following five preparations of lidocaine: 1) plain 1% lidocaine; 2) plain 1% lidocaine plus epinephrine (added by investigator); 3) commercial 1% lidocaine with epinephrine already added; 4) sodium bicarbonate added to commercial 1% lidocaine with epinephrine; and 5) sodium bicarbonate added to plain 1% lidocaine.

We added 0.05 ml of a commercial 1:1000 solution of epinephrine solution to each 10 ml of local anesthetic to yield a final concentration of 1:200,000. One ml of sodium bicarbonate (1 mEq/ml) was added to each 10 ml of local anesthetic to give a final concentration of 0.1 mEq/ml. The amount of sodium bicarbonate added to the solution was calculated from previous titration data on lidocaine solutions with sodium bicarbonate (McKay WR, Hord AH, unpublished data). The pH values were measured with a Corning 140 pH meter; two samples of each preparation were tested in triplicate.

Six discrete areas on the volar surface of the left forearm served as sites for injection of the test preparations. A random numbers table was used to assign preparations to each of the areas. Before injection, the skin was cleaned with 70% isopropyl alcohol and allowed to dry. For each test 0.1 ml was injected intradermally and then 0.2 ml injected subcutaneously via a 26 gauge hypodermic needle and 1 ml tuberculin syringe in one injection. Neither subject nor experimenter was aware of syringe contents. All six injections were made at 15 sec intervals covering approximately a 2-min period. Immediately after all six injections, subjects were asked to score pain elicited, using a 10 cm linear analog pain scale (5–7). Subjects were instructed to score a pain-free injection as 0 and the most pain imaginable as 10. Scores were then measured to the nearest mm. Highest and lowest pain scores were used to rank agents as most or least painful.

The Kruskall-Wallis analysis of variance was used to examine the distribution of pain scores among agents, and the Wilcoxon Signed Rank test employed

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Table 1. P Values for Paired Comparison of Preparations

	Lidocaine + bicarbonate	Epinephrine + bicarbonate	Saline	Added epinephrine	Plai
Commerical lidocaine + epinephrine	0.00008[a]	0.001[a]	0.007[a]	0.007[a]	0.07
Plain lidocaine	0.0001[a]	0.002[a]	0.01[a]	0.09	—
Lidocaine + added epinephrine	0.0003[a]	0.08	0.4	—	—
Saline	0.002[a]	0.005[a]	—	—	—
Lidocaine + epinephrine and bicarbonate	0.005[a]	—	—	—	—

[a] $P < 0.05$.

to contrast pairs of agents. Mean pain scores are reported with the standard error of the mean (SEM). A probability (P) value of ≤ 0.05 was considered statistically significant.

Results

The commercial preparation of lidocaine with epinephrine had the highest mean pain score (43 ± 5); this was more painful than was plain lidocaine (38 ± 5), plain lidocaine with added epinephrine (30 ± 4), normal saline solution (29 ± 4), commercial preparation of lidocaine and epinephrine with sodium bicarbonate (24 ± 4), or lidocaine with sodium bicarbonate (15 ± 3).

Analysis of variance indicated a significant nonrandom distribution with a P value of 0.001. Both lidocaine with commercial epinephrine and plain lidocaine were significantly more painful than normal saline or the two lidocaine preparations containing sodium bicarbonate. Plain lidocaine with sodium bicarbonate was significantly less painful than all others. The pain response to plain lidocaine did not differ statistically from pain responses to lidocaine–epinephrine solutions without bicarbonate. The probability values of all paired comparisons are shown in Table 1.

Twelve of the 24 subjects considered commercial lidocaine with epinephrine to be the most painful whereas six considered plain lidocaine the most painful preparation. The two bicarbonate-containing preparations accounted for 20 of the "least painful" responses. Sixteen subjects considered plain lidocaine with sodium bicarbonate to be the least painful; none considered it most painful. In fact, the addition of sodium bicarbonate to plain lidocaine preparations resulted in a 61% reduction in mean pain score. Addition of sodium bicarbonate to the commercial preparation of lidocaine and epinephrine resulted in 24% reduction of mean pain score (Fig. 1).

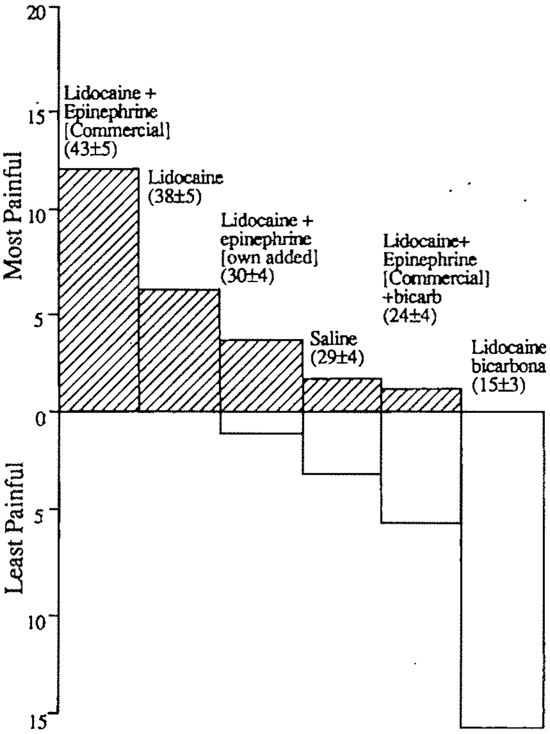

Figure 1. Frequency of subjects considering agent most painf (hatched bars) or least painful (open bars). Numbers in parenthese at top of bar are mean pain scores ± SEM.

Discussion

Our study demonstrates that pain resulting from ski infiltration of lidocaine solutions with or without epi nephrine can be diminished by the addition of sodiu bicarbonate. The mechanism of this decrease in pai is unknown, but probably relates to an increase i pH.

If H^+ ions themselves cause pain, sodium bicar bonate would decrease pain merely by decreasing H concentration. Consistent with this idea, commercia lidocaine with epinephrine (pH 4.15) has a lower p

Table 2. Properties of Preparations Tested

	pH	Sodium chloride (mg%)	Additives
Lidocaine + commercial epinephrine	4.05	0.7	Sodium metabisulphite (0.5 mg/cc)
Lidocaine	6.49	0.7	—
Lidocaine + added epinephrine	6.39	0.7	—
Normal saline	6.85	0.9	—
Lidocaine + epinephrine + bicarbonate	7.37	0.7	Sodium metabisulphite (0.5 mg/cc)
Lidocaine + bicarbonate	7.38	0.7	—

and is more painful than is lidocaine with added epinephrine (pH 6.4) (Table 2). However, the cause of pain on skin infiltration is probably more complex and depends on factors other than pH alone. For example, procaine (pH 4.3) is more acidic but less painful than is lidocaine (pH 6.3) (2). Also, the strongly acidic preparation, 2-chloroprocaine (pH 3.0) is no more painful than is lidocaine (unpublished observations).

Alternatively, the pain-reducing effect of sodium bicarbonate may represent a shift of the equilibrium between ionized and nonionized forms of lidocaine, favoring formation of the nonionized form. Conceivably, nociceptive receptors may be less sensitive to the nonionized form. Conversely, the greater diffusability of the nonionized form may result in rapid inhibition of pain transmission, thereby preventing nociceptive impulses from being fully appreciated. Thus, factors other than pH, such as intrinsic properties of local anesthetics, may play an important role in the pain response to local anesthetics. Further studies will be required to elucidate the mechanisms of local anesthetic-induced pain.

In conclusion, the addition of sodium bicarbonate significantly reduces pain produced by infiltration of lidocaine with or without epinephrine. The means by which the pain is reduced probably relates to the alkalinity of solutions of local anesthetic.

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Ketanserin and Guanethidine in the Treatment of Causalgia

John A. H. Davies, FFARCS, Trevor Beswick, MSc, MPS, and Graeme Dickson, FFARCS

Reflex sympathetic dystrophies such as causalgia are notoriously difficult to manage even when treatment is started early. Treatment after the condition has been present for more than a year results in a success rate of less than 5% (1). Vasodilatation is not uncommon in the early months but the established condition invariably contains an element of vasoconstriction. Treatment is mainly directed at reducing painful transmission with local anesthetic agents and improving the circulation. We report a patient who, after having 75 guanethidine intravenous regional blocks for causalgia, was successfully treated with ketanserin.

Case Report

A 55-yr-old woman attended our pain clinic for 9 yr suffering from causalgia in her left foot that had developed subsequent to trauma 12 yr before she came to us. Several operations, including a lumbar sympathectomy, had produced no relief. During the past 8 yr, she had had 75 intravenous regional blocks with guanethidine (10–25 mg). The technique used was that described by Hannington-Kiff (2). This was at first intolerably painful and required general anesthesia with halothane on each occasion. Subsequently, the addition of 20 ml 0.25% bupivacaine to the guanethidine enabled the patient to tolerate the procedure without general anesthesia. Each block relieved her pain for 3–5 weeks.

After a full discussion with the patient and having obtained her informed consent, we gave her 14 mg ketanserin systemically by intravenous injection. Subjectively and objectively her affected foot became noticeably warmer within 30 min of the injection. Within an hour, the patient reported that the pain in her affected limb was reduced and mobility in her toes was improved. The major side effect noted was postural hypotension that persisted for approximately 2 hr, after which she was well enough to return hom She also complained of transient nasal congestion an a dry mouth. This treatment was followed by or ketanserin. Initially, she took 60 mg daily in divide doses, which was gradually increased to 80 mg dail in divided doses. Side effects after oral treatment wer minimal with no recurrence of postural hypotensio

For the past 12 months, she has not required fu ther intravenous treatment with guanethidine. He affected foot has remained warm and her pain co trolled to the extent that she has returned to full-tim employment.

Comment

The technique of intravenous regional guanethidin block as described by Hannington-Kiff (2) has prove to be an effective treatment of causalgia. Howeve its disadvantages include the need to employ a re gional intravenous technique to restrict the guaneth idine to the affected part and to prevent hazardou systemic effects. It also requires admission to the hos pital on an outpatient basis. We suspect our patie is unique in having had a total of 75 treatments. Thes were well tolerated with no serious side effects, bu provided relatively short-lived relief of her pain.

The postulated role of 5-hydroxy tryptamine in ca salgia suggests that ketanserin, a specific 5-HT a tagonist, may be beneficial. Preliminary work (3) ha shown that ketanserin appears to restore the periph eral circulation, reduce pain, and improve the fun tion of the affected limb in causalgia. In our patien the drug was given as a single simple systemic intr venous injection followed by oral treatment. Its us in this patient eliminated the need to admit her to th hospital for frequent repeated invasive techniques an has provided better and more continuous pain co trol.

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Tension Pneumoperitoneum–Pneumothorax during Repair of Congenital Diaphragmatic Hernia

James H. Diaz, MD

Pneumoperitoneum and pneumothorax are common consequences of pulmonary barotrauma during mechanical ventilation in neonates. Neonatal pneumoperitoneum during assisted ventilation is frequently described in association with bowel perforations, especially gastric perforation, and extrapleural air leaks, especially pneumomediastinum and pneumopericardium (1–5). Neonatal pneumothorax occurs more commonly during positive pressure ventilation of infants with reduced lung compliance or interstitial emphysema. Positive pressure ventilation and nitrous oxide administration will rapidly expand either thoracic or peritoneal air promoting cardiac compression with reduced myocardial contractility and diminished venous return to the heart (tension effect). Unlike tension pneumothorax, tension pneumoperitoneum is an infrequent cause of acute ventilatory insufficiency and cardiac arrest in infants and children (6). Only early recognition and percutaneous decompression of combined tension pneumothorax and tension pneumoperitoneum will permit effective cardiopulmonary resuscitation (6). Combined tension pneumoperitoneum–pneumothorax (TPP) with cardiac arrest in a newborn with congenital diaphragmatic hernia is reported. Pathophysiologic mechanisms, predisposing factors, and management of TPP are discussed.

Case Report

A 2700-g, full-term male infant with Apgar score 2/4 was scheduled for immediate repair of a congenital left diaphragmatic hernia. Since birth 2 hr prior to surgery, the infant had required tracheal intubation (3.0-mm internal diameter oral endotracheal tube), controlled mechanical ventilation, and intermittent intravenous bicarbonate infusion for respiratory fai ure with progressive acidosis.

On arrival in the operating room, the infant wa normothermic but cyanotic and bradycardic. Atr pine, 0.04 mg, and pancuronium, 0.4 mg, were a ministered intravenously, and hand hyperventilatio with 100% oxygen was begun using a Mapleson nonrebreathing circuit with a fresh gas flow of 5 L/mi Peak inspired pressures of 20–30 cm H_2O (mean ai way pressure of 10–15 cm H_2O) were confirmed ma ometrically at the tracheal tube, and initial intraope ative measurement of blood gas tensions showed pH of 7.19, Pa_{O_2} 38 mm Hg, Pa_{CO_2} 60 mm Hg, an base deficit −10 mEq/L. During skin preparation, th apical pulse, which had been restored to 150–1 beats/min by intravenous atropine, again decrease to 60 to 80 beats/min. Breath sounds were lost ov the right chest, subcutaneous emphysema develope in the right axilla, and rapidly progressive abdomin distension occurred (Fig. 1). Umbilical artery pre sures became unobtainable and mechanical ventil tion was impossible.

Closed cardiac compression was begun and the fo lowing drugs were administered intravenousl $NaHCO_3$, 3.0 mEq; atropine, 0.04 mg; $CaCl_2$, 30 m epinephrine, 30 μg; and isoproterenol, 20 μg. A 2 gauge plastic cannula was inserted in the right a terior second intercostal space to decompress su pected right tension pneumothorax (Fig. 2). A secon 20-gauge plastic cannula was then inserted along th linea alba midway between the symphysis pubis an umbilicus to decompress suspected tension pne moperitoneum that did not resolve with chest a drainage (Fig. 2). Audible air leaks from both cannula confirmed suspected diagnosis of TPP (Figs. 1 and 2 Cardiac output was rapidly restored, a right anteri chest tube was inserted, and left diaphragmatic r construction using a Gore-Tex® patch was carried o through a left subcostal incision. Measurement of a terial blood gas tensions during diaphragm reco struction showed the pH to be 7.29, Pa_{O_2} 40 mm H Pa_{CO_2} 50 mm Hg, and base deficit −5 mEq/L.

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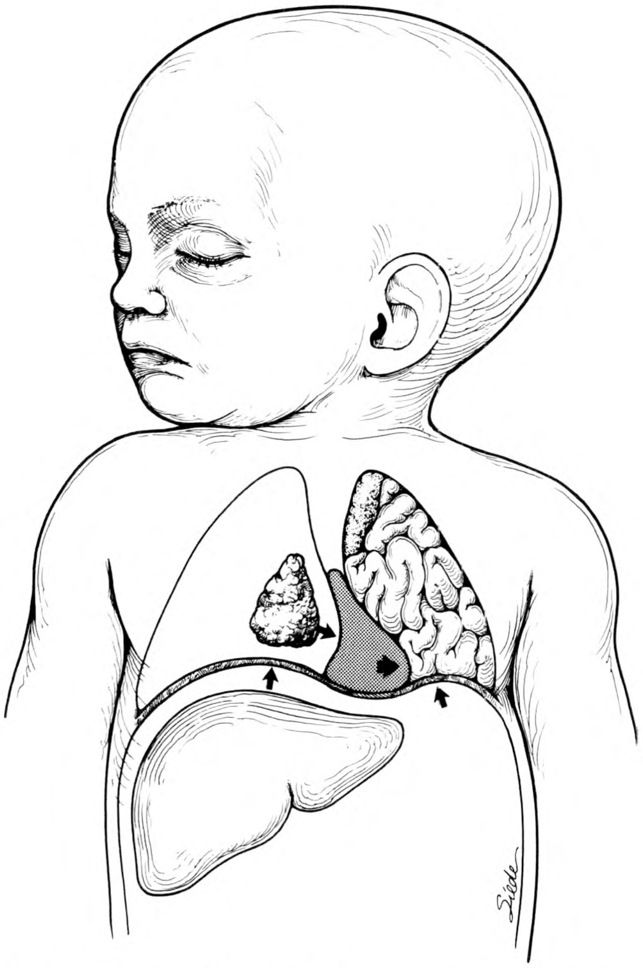

Figure 1. The pathophysiologic effects of tension pneumoperitoneum–pneumothorax (TPP) in the neonate include mediastinal shifting and diaphragm elevation with restricted ventilation, reduced thoracic venous return, and cardiac compression with acute hemodynamic compromise.

After surgery, the infant was transferred to the neonatal intensive care unit where a continuous infusion of tolazoline was begun to improve systemic oxygenation. The patient died of progressive hypoxemia and irreversible metabolic acidosis 6 hr postoperatively. Autopsy documented left diaphragmatic agenesis, severe bilateral pulmonary hypoplasia, preductal coarctation of the aorta, and ventricular septal defect.

Discussion

Expanding TPP with cardiac arrest is an intraoperative emergency that must be managed by rapid percutaneous decompression of both the affected hemithorax and the peritoneal cavity (3). The rapid intraabdominal accumulation of air during TPP may elevate the hemidiaphragms to such an extent that ventilation is

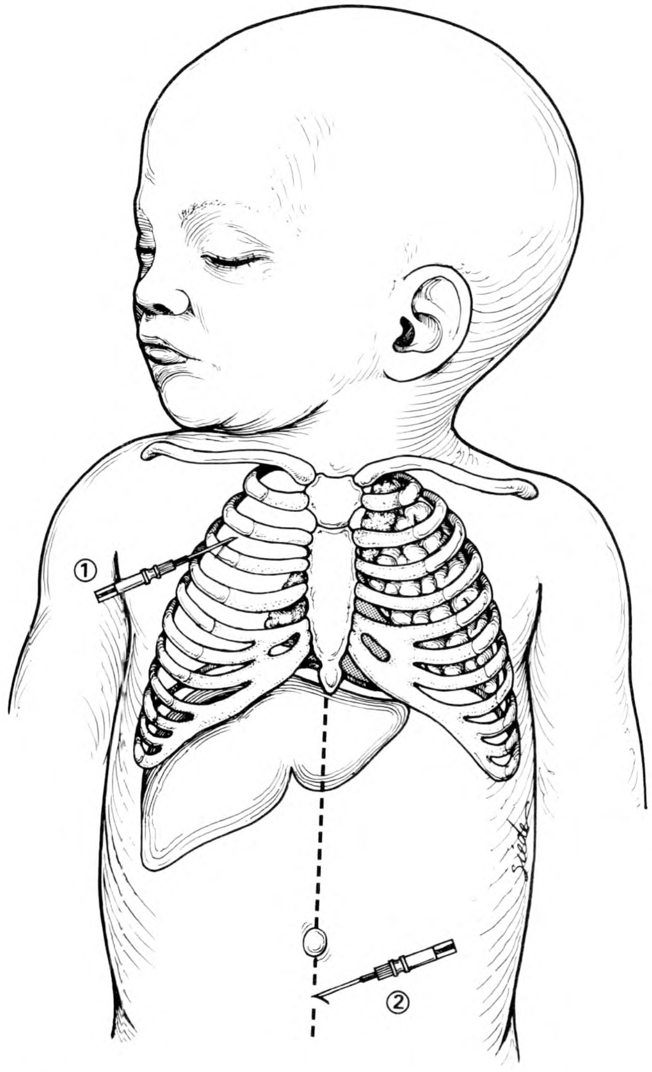

Figure 2. Acute management of TPP in the neonate should include: 1) cannula decompression of the breathless hemithorax followed by 2) cannula decompression of the peritoneal cavity if chest drainage does not relieve abdominal distension quickly. Tube thoracostomy should be provided immediately after hemodynamic stabilization. Continued abdominal distension despite chest drainage suggests the need to provide for peritoneal air drainage and to exclude bowel perforation.

Table 1. Factors Predisposing to TPP in Neonates from Extrapleural Air Leak

1. Recent tracheostomy
2. Reduced pulmonary compliance
   - A. Respiratory distress syndrome
   - B. Bronchopulmonary dysplasia
   - C. Diaphragmatic hernia
3. Intermittent small airways obstruction
   - A. Meconium aspiration syndrome
   - B. Foreign body aspiration
4. Emphysema
   - A. Pulmonary interstitial emphysema
   - B. Congenital lobar emphysema
   - C. Congenital lung cysts

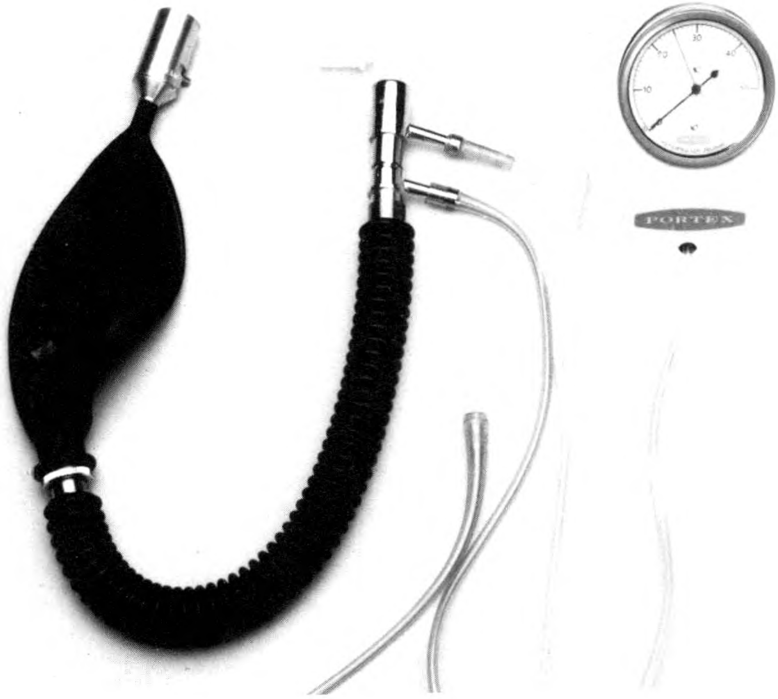

Figure 3. Simple system for continuous manometric monitoring of delivered airway pressures in an infant nonrebreathing anesthesia circuit, such as a Jackson Rees (as shown), Mapleson D, or Bain circuit.

impeded, thoracic venous return reduced, and cardiac output diminished (Fig. 1) (7). The rapid intrathoracic accumulation of air during TPP will also compress the heart and diminish venous preload by shifting the mediastinum away from the thoracic air leak (Fig. 1). Hypercapnia, hypotension, and cardiac dysrhythmia or asystole will quickly ensue with TPP.

Intraabdominal air during TPP may result from perforation of an air-containing viscus, either lung, stomach, or bowel, or from retroperitoneal air dissection from a pneumomediastinum, pneumothorax, pneumopericardium, or combined air leaks (1–4,6–8). Neonatal pneumoperitoneum alone has even been reported without significant adventitious pulmonary air (5).

The simultaneous appearance of air in the pleural and peritoneal cavities during positive pressure ventilation is usually not due to the presence of a perforated abdominal viscus (9). Absence of peritoneal fluid, normal thickness of bowel wall, and lack of intestinal air fluid levels provide additional radiographic confirmation of nonsurgical pneumoperitoneum (9).

Factors predisposing to intrathoracic air during TPP include recent tracheostomies, disorders of reduced pulmonary compliance, intermittent small airways obstruction, and emphysema (Table 1) (1,4,6–8). Neonates with congenital diaphragmatic hernia are particularly susceptible to pneumothorax on the side opposite intestinal herniation because of bilateral lung compression and hypoplasia, poor pulmonary and chest wall compliance, and an early need for rapid mechanical ventilation to manage respiratory failure and acidosis (Fig. 1). Any extrapleural air leak may be easily expanded by positive pressure ventilation, nitrous oxide inhalation, or upper airway obstruction with development of high transpleural pressures (6,10,11).

The key to successful management of TPP is suspicion, early recognition, airway protection by endotracheal intubation, discontinuance of nitrous oxide inhalation, immediate thoracic then abdominal decompression, and provision for continued air egress by chest tube during positive pressure ventilation (Fig. 2) (6,10,11). Radiographic confirmation of extrapleural and peritoneal air or endoscopy to rule out gastrointestinal perforation may waste valuable time and is not necessary to institute emergency decompression of suspected TPP with cardiac arrest.

Acute abdominal distension during mechanical ventilation in neonates may occur with tension pneumothorax alone as the diaphragm, liver, and intestines are pushed downward and does not necessarily indicate tension pneumoperitoneum or TPP. Attempted abdominal decompression by cannula or trocar in such a situation could lacerate abdominal viscera. If immediate abdominal decompression is indicated for effective CPR in TPP without prior radiographic evaluation, it must be carried out only after the complete evacuation of air from the breathless hemithorax fails to relieve both respiratory distress and abdominal distension (Fig. 2).

During surgical procedures in infants with the disorders listed in Table 1, attention should be directed toward assuring the continued presence of clear bilateral breath sounds, the absence of subcutaneous emphysema or abdominal distension, and the maintenance of low mean airway pressures (6). Elective tracheostomies in children undergoing lengthy operations should be performed primarily for maintenance of the airway rather than for ventilation and, if necessary, should be performed as close to the end of the surgical procedure as possible to avoid barotrauma from prolonged mechanical ventilation (6). Continuous manometric monitoring of peak inspired and mean airway pressures at the tracheal tube is recommended in infants predisposed to TPP from extrapleural air leak (Table 1, Fig. 3).

Finally, if preoperative pneumoperitoneum or pneumothorax with impending ventilatory distress is present, abdominal or thoracic decompression by cannula or trocar should be undertaken after radiographic confirmation and before induction of anesthesia with positive pressure ventilation and nitrous oxide inhalation (12). As noted, intraoperative thoracic air egress by chest drain should be provided early in the management of TPP and usually relieves the associated nonsurgical pneumoperitoneum as well.

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ANESTH ANALG 5
1987;66:581–586

Letters to the Editor

A Device for Uniform Testing of Sensory Neural Blockade during Regional Anesthesia

To the Editor:

Anesthetists and anesthesia students use many different ways to measure the extent of sensory neural blockade after regional anesthesia. Alcohol swabs, very fine needles (gauge 23 or 25), very large needles (gauge 18 or 19, or an epidural needle), safety pins, screwdrivers, or clamps are all used. The thorn of a thistle was recommended by von Frey as the stimulus to test sensory analgesia "since these thorns have a very constant degree of sharpness" (1). Some anesthetists use their fingernails to pinch patients to test the presence of sensory blockade (2). The intensity of the stimulus resulting from this wide assortment of methods is variable and may not be uniformly reproducible. In the everyday practice of anesthesia, uniformity and reproducibility may not be imperative. However, when doing a research project where several repeated assessments are required, e.g., to determine when maximum level of sensory anesthesia is achieved and when two-segment sensory regression occurs, uniformity in testing and reproducibility from investigator to investigator become important. For this reason, we designed an inexpensive and practical device for measuring sensory anesthesia using pinprick sensation.

This device is made by pushing the pointed end of a large open safety pin through a rubber stopper obtained from a vacutainer (Fig. 1). A length of 7–8 mm protruding out on the opposite side of the rubber stopper is usually adequate to produce a definite sensation of pinprick without causing discomfort. To be sure of the adequacy of stimulus without producing pain, it is advisable to test the device on oneself. While the pointed end of the pin is used to test for dermatomal extent of sensory anesthesia, the blunt head of the same pin can be used to provide the patient a sensation of pressure so as to enable the patient to distinguish between pain and pressure sensations. The safety pin should be opened to a 90° angle and held at the head end during testing (Fig. 2). It is important for the rubber stopper to be pushed flush to the skin in order to be sure that the pointed end of the safety pin is in direct contact with the area being tested.

Ten anesthetists tried the device on themselves and each other and all agreed that the stimulus produced w adequate and similar when applied to various body par None of the anesthetists incurred any scratches or nee punctures despite pushing the device firmly against t skin. The edges of the rubber stopper prevent the pin fr being pushed too far to the point of hurting or penetrati the skin. This is an important feature of this device fo the area being tested is anesthetized, skin puncture a abrasion can be produced without the patient being aw of the damage until some time later (3).

The accuracy of this device was compared with the ot frequently used sensory stimuli, namely a 25-gauge need a 19-gauge needle, an open safety pin, and an alcohol sw by testing twenty patients receiving epidural anesthesia a variety of procedures. The sensory level detected by t device compared very well with those of the three ot pointed instruments. However, when the level of sens anesthesia noted with pinprick sensation was compar with that at which cold temperature discrimination is lo a difference of two to three dermatomal segments was c sistently observed similar to the differential blockade se in spinal anesthesia (4).

Reproducibility of results obtained using this device w established by asking three different anesthetists to use t device in ten patients. There was 100% concurrence wh the results of their independent determinations on the sa patient were compared.

None of the 30 patients tested using this device show any skin scratches or red marks at the time of the po anesthetic visit.

We recommend the use of this device for testing t extent of sensory anesthesia when performing experime and in the day-to-day practice of anesthesia. It is safe, expensive and easy to assemble. Use a different safety p for each patient to avoid cross contamination.

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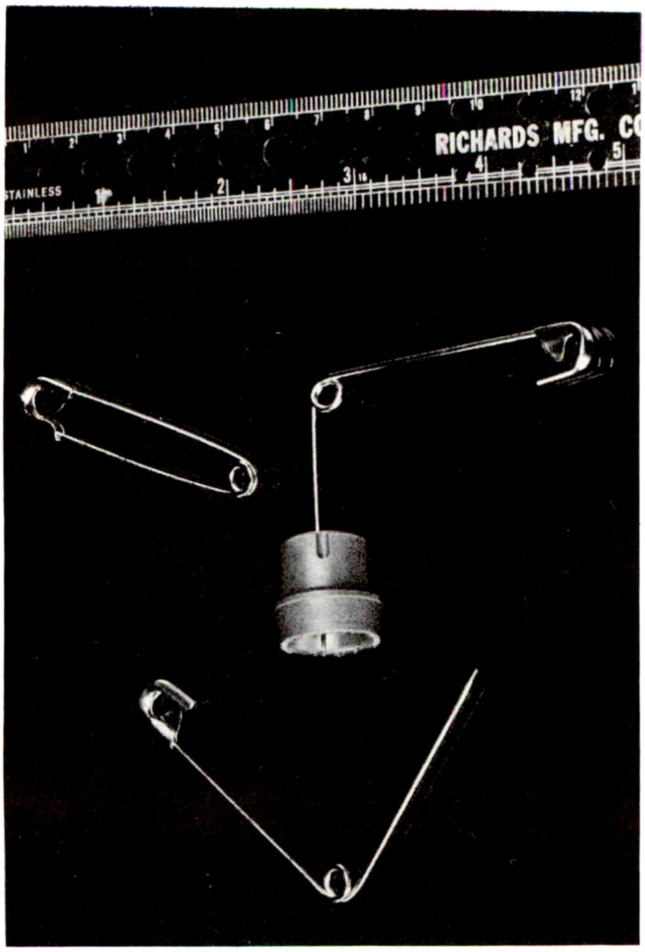

Figure 1. Device made by pushing large safety pin opened at a 90° angle through a rubber stopper.

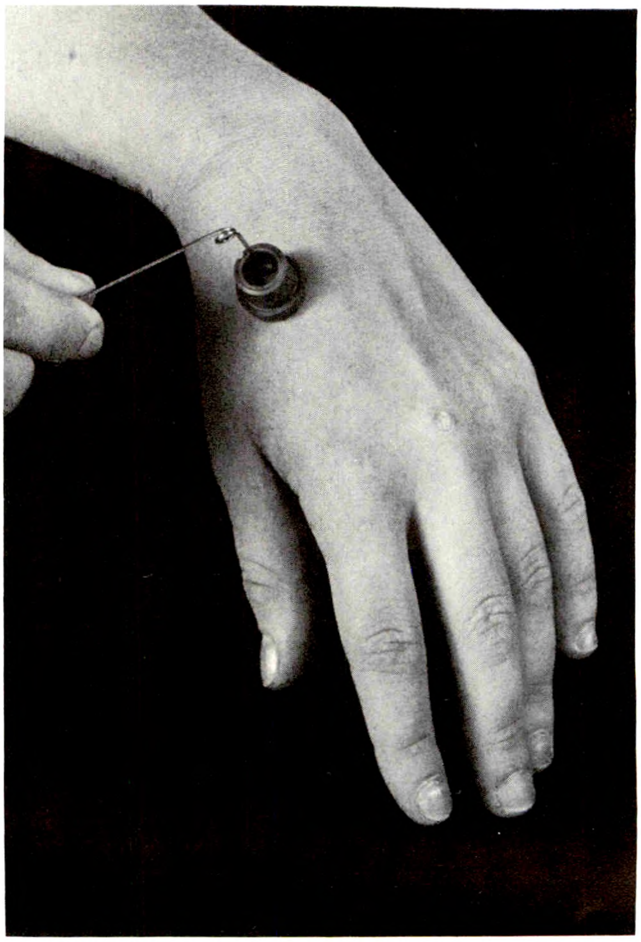

Figure 2. Device shown held at the head of the safety pin and pushed flush to the area being tested.

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Spinal Anesthesia and Myocardial Ischemia

To the Editor:

Urmey and Lambert (1) described the reversal of myocardial ischemia after administration of spinal anesthesia. They presumed that decreases in blood pressure (140/80 to 105/? mm Hg) and heart rate (105 to 95 beats/min), observed after onset of the spinal block, reduced myocardial oxygen consumption, while a possible decrease in preload could have contributed in reversing the myocardial ischemia. However, myocardial ischemia was observed again 12 hr postoperatively, when almost identical blood pressure and heart rate were present as after the onset of the spinal block (102/80 mm Hg, 96 beats/min), indicating that the decreases in blood pressure and heart rate were not the most important factors in reversing the myocardial ischemia.

In our opinion, the decrease in preload (which was not measured, however) was the crucial factor in reversing myocardial ischemia. The decrease in preload results from sympathetic denervation on the venous site of the circulation (2). This has positive effects on myocardial ischemia by improving subendocardial blood flow, decreasing myocardial oxygen consumption by decreasing afterload (afterload depends on systolic blood pressure, left ventricular end-diastolic volume, and wall thickness), and by decreasing heart rate (2). Contributing factors may have been the decrease in blood pressure and heart rate, and possibly also a decrease in coronary vascular tone or even the relief of coronary artery spasm by decreased circulating cathecholamine levels (3,4).

Regional anesthesia can indeed be administered safely in a patient with acute myocardial ischemia, but only if adequate monitoring is provided. It is unsafe to create significant hemodynamic changes in such a patient without sufficient hemodynamic monitoring: the presence of hypovolemia would have caused severe hypotension with disastrous effects, because treatment is difficult (2). However, we suspect that this patient had borderline congestive heart failure. This could explain the absence of hypotension after onset of the block (flat Starling curve) and the occurrence of fulminant congestive heart failure postoperatively after administration of a single dose of atenolol (50 mg by mouth), requiring inotropic support, intubation, and mechanical ventilation for 2 days. It is possible that centralization of peripheral venous blood after disappearance of the sympathetic block was a contributing factor. Hemodynamic monitoring would have revealed the borderline congestive heart failure, so that the postoperative complications could have been prevented.

Regional anesthesia can be a good technique in a patient who requires emergency surgery in the presence of acute myocardial ischemia. If spinal anesthesia is chosen, it might be better to use a hyperbaric local anesthetic solution, because this technique allows more control over the spread of anesthesia by appropriate positioning of the patient (5). However, an epidural anesthetic would be preferable because it gives a slower onset of the sympathetic block in comparison with spinal anesthesia, making hypotension less likely to occur or easier to treat (6,7). An epidural catheter technique allows even better control of anesthetic level and reduces the risk of a systemic toxic reaction compared to a "one shot" epidural technique (8,9).

In conclusion, we agree with the authors that regional anesthesia can be a good technique in a patient with acute myocardial ischemia. However, epidural anesthesia may be preferable over spinal anesthesia because it may provide easier control of hemodynamic changes. In addition, it is important that regional anesthesia in a patient with acute myocardial ischemia be accompanied by the same invasive monitoring that would be used if general anesthesia is given, and by adequate sedation.

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Perioperative Myoclonia or Seizures

To the Editor:

The case report of seizures after isoflurane anesthesia (1) of great interest. However, it also raises another concen because postoperative movements of shoulders and arm are so often labelled as "myoclonic seizure" without an information about the frequency, progression, pattern, EEC or any associated postictal phenomena.

Myoclonus is a movement disorder and both positiv and negative myoclonus can occur from a lesion in any pa of the neuraxis (2). Depending upon the EEG findings, myoclonus is divided into epileptic and nonepileptic type Epileptic myoclonus or myoclonic seizures accompany distinct group of progressive neurologic disorders assoc ated with dementia and include chronic viral, degenerativ and metabolic diseases. Some of the syndromes include under myoclonic seizures are Uverricht–Lundberg diseas Baltic myoclonus, Jakob–Creutzfeldt disease, subacute scl rosing panencephalitis, West syndrome, juvenile myoclonus, and Lennox–Gaustaut syndrome (3,4). Myoclonu can also be associated with idiopathic epilepsy and epileps partialis continua (5).

Nonepileptic myoclonus also has a variety of present tions, including dystonic myoclonus (6), periodic tremo of sleep (7), segmental myoclonus and multifocal myoclonus (8). Segmental myoclonus is mostly rhythmic, h a frequency of 1–3 Hz, and originates from brainstem c spinal cord (9). Spinal segmental myoclonus is produce by unchecked spinal neuronal discharge as a result of di inhibition of supraspinal control. A major role in the spin form is played by abnormal discharges from interneuron and gamma motor neurons (10,11). Multifocal myoclonu not characterized by any particular EEG pattern, consis of sudden nonrhythmic and nonpatterned twitching of th proximal muscles. It occurs in stuporous or comatose p tients with severe metabolic disturbances, including CC narcosis and hyperosmolar states (8).

Certain inhalation and intravenous anesthetics, i.e., ether enflurane, ketamine, and etomidate, have been shown t produce seizure activity on the EEG and have the potenti to initiate a perioperative seizure (12–18). Even though fentanyl and isoflurane have also been implicated with respe to perioperative "seizures" (1,19–22), neither of these agent produce EEG seizure activity (23,24). Seizures associate with fentanyl and isoflurane are most likely segmental o multifocal myoclonia, both of which represent the brain stem or spinal cord effect of a variety of CNS depressants

The important point is that epileptic and nonepileptic myoclonus have different diagnostic, therapeutic, and prognostic implications. A plea may be made that unless EEG changes or other postictal phenomena can be clearly demonstrated, one should not label perioperative movement disorders or myoclonia as "seizures". Perhaps "perioperative myoclonia" or "perioperative movement disorder" might be an appropriate term to describe such phenomena.

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Trimethaphan Is Useful for the Parturient Requiring Neuroanesthesia

To the Editor:

In their report "Induced Hypotension for Clipping of a Cerebral Aneurysm during Pregnancy," Newman and Lam (1) state that trimethaphan (TMP) is unsuitable for these cases because it reduces cardiac output and cerebral blood flow. In doing so, they cite a canine study by Stoyka and Schutz (2) showing a decrease in cardiac output with TMP. No mention was made of cardiac filling pressures or of intravenous fluids administered during the experiment. Cook et al. (3) and Nitter-Hauge (4), in human studies, have shown that patients with adequate cardiac filling pressures have no decrease in cardiac output with TMP. Other studies advocate TMP for increasing cardiac output in patients with congestive heart failure (5,6) or after cardiac surgery (7).

Newman and Lam are correct in stating that TMP decreases cerebral blood flow (2). Turner et al. noted that this reduction results in a stable intracranial pressure (8). This is in contrast to those agents that may increase both cerebral blood flow and intracranial pressure. An example is isoflurane, which under the normocapnic conditions used by Newman and Lam produces increased intracranial pressure (9). Moreover, Smith and Marque (10) have shown a linear relationship between cerebral blood flow and brain water content in dogs after a cerebral injury.

Further advantages of TMP are noted by Abouleish (11) who suggests that it may be the intravenous hypotensive agent of choice in the parturient requiring neurosurgery because of its rapid hydrolysis and lack of harmful effects on the fetus.

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In Response:

In defending the use of trimethaphan (TMP) for the parturient, Dr. Sosis has raised a very important issue in neuroanesthesia, but at the same time I believe he has missed the message in our report.

Although the study by Stoyka and Schutz was carried out in dogs, and the filling pressures were not mentioned, it must be pointed out that this was a comparative study between TMP and sodium nitroprusside (NTP). Despite similar fluid therapy in both groups, the decrease in cardiac output in the TMP group contrasted sharply with the unchanged cardiac output in the NTP group, indicating that TMP has negative inotropic properties (1). Indeed such properties of TMP had been confirmed in another canine study (2). The adverse effect of TMP on cardiac output during anesthesia has also been reported in human studies (3,4). In contrast, the studies quoted by Sosis were performed on unanesthetized patients with cardiac disease, and it is a well known fact that patients in heart failure can improve their cardiac output simply by virtue of afterload reduction with decrease in systolic blood pressure. Fahmy and Soter did demonstrate unchanged cardiac output in one anesthetic study, although only relatively mild hypotension was produced in their study (5).

Perhaps whether or not TMP affects cardiac output is trivial compared to its known deleterious effect on cerebral blood flow (CBF). Dr. Sosis agreed with me on this point and correctly stated that the decrease in CBF results in a stable intracranial pressure (ICP). But I submit that when induced hypotension is employed during craniotomy for aneurysm, the concern is with maintenance of CBF and not control of ICP as the latter should be zero after the opening of the dura. That TMP is unsuitable for induced hypotension has been convincingly demonstrated in studies (animal as well as human) examining the blood pressure threshold below which cerebral electrical activity is adversely affected; the threshold is consistently higher with TMP compared to NTP (6,7). In another study, cortical activity was better maintained during oligemic hypotension than TMP-induced hypotension (8). Although there was no similar, comparative study with isoflurane-induced hypotension, Newman et al. demonstrated that CBF is maintained during isoflurane-induced hypotension in humans (9). In addition, cerebral oxygen tension, at least in rats, is higher during hypotension induced with isoflurane compared to NTP (10). In contrast, TMP-induced hypotension results in an even lower brain surface oxygen tension than NTP (11). Moreover, the pupillary dilatation associated with use of TMP makes it difficult to assess the neurologic status of the patient in the postoperative period.

However, that is not to say TMP should never be used in the parturient. On the contrary, because of its effect on CBF and ICP, it may well be the drug of choice for blood pressure control in severely preeclamptic patients, as pointed out by Sosis and Leighton in a previous communication (12).

In short, successful pharmacologic therapy depends no only on intimate knowledge of the drug but also the indication for which it is used; TMP may be a useful agent for acute blood pressure control in preeclamptic patients, bu is unsuitable for induced hypotension in neurologic disorders unless hypotension is required in a patient with preexisting increased ICP prior to opening the dura (for which I know of no indication).

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High Frequency Ventilation

To the Editor:

The case report by Biondi et al. (1) may cause continuing confusion about terminology concerning high frequency ventilation. From the description of ventilatory circuitry, i is clear that jet ventilation was used.

Several recent reviews (2–4) offer definitions and terminology for high frequency ventilation, promoting bette comparison and evaluation of the different available high frequency ventilators and of the situations in which they are used. From these reviews it is to be concluded that the term high frequency positive pressure ventilation should be reserved for ventilation at frequencies between 1 and 2 Hz, employing a specific ventilator with pneumatic valve. Furthermore, in the paper by Biondi et al. no specification is presented on how PEEP was given.

Although inadvertent PEEP may be elicited by high frequency ventilation due to the chosen ventilator settings (5), it is improbable from the data reported in their article that the jet ventilation resulted in a PEEP of 10 cm H_2O.

In the discussion the authors mention that their study indicates that high frequency ventilation can maintain transthoracic and transpulmonary pressures at subambient levels. However, no measurements relating to these variables are presented. It might be worthwhile to elucidate these points in order to clarify the discussion about high frequency ventilation and prevent "the impression that high frequency ventilation magically reduces or eliminates the deleterious effects of IPPV (6)."

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In Response:

In response to the letter by Tamsma, no unanimous classification of high frequency ventilatory techniques has been determined. Our system of high frequency jet ventilation (HFJV) was performed according to the methods described in the text. This system of ventilation employed the use of a solenoid interruptor of high pressure gas flow that was delivered to the proximal airway via a 1.7-mm cannula at a rate of 2.5 Hz.

Positive end-expiratory pressure (PEEP) and entrained fresh gas flow was delivered via an auxillary circuit using a conventional positive pressure balloon type mushroom valve in series with a Bear I^R ventilator (Bear Medical Systems, Riverside, CA). Autopeep in this system, although detectable, was minimal (1–2 cm H_2O).

In reference to the question of transthoracic pressure measurements, numerous investigators (1) have shown that transpulmonary and transthoracic pressures are reduced during HFJV. However, there are data (2) to suggest that alveolar and mean intrathoracic pressures may actually increase during HFJV. These effects are more commonly observed when HFJV is applied to patients with obstructive lung disease with increased airway resistance and increased pulmonary compliance, which produces dynamic alveolar gas trapping secondary to impedance to expiratory gas flow (3). In fact, Kolton et al. (4) have demonstrated that HFJV, as opposed to conventional positive pressure ventilation, may allow large increases in lung volume at comparable transpulmonary distending pressures because of the hysteresis between the static and dynamic transpulmonary pressure–lung volume relationships. However, all of these conditions that markedly increase lung volume are associated with decreased biventricular preload and decreases in cardiac output.

Transpulmonary and transthoracic pressure measurements were not performed in the case reported. Low mean airway pressures, minimal autopeep, and the absence of changes in cardiac output in this patient during HFJV at driving pressures <30 psi would make significant increases in transpulmonary or transthoracic pressures unlikely.

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Book Reviews

Current European Anesthesiology: The Yearbook of the European Academy of Anesthesiology, Volume 2

R. M. Jones, ed. New York: John Wiley, 1986, 308 pp, $48.00.

Any collection of abstracts suffers from the problem of "making hungry where most it satisfies." This second annual offering from the European Academy of Anesthesiology summarizes 170 published papers regarded as the most significant contributions to the 1985 European journals. The contributions have been chosen by a distinguished panel of editors and are divided into sections covering the major anesthetic subspecialties. Although these abstracts are more detailed than many others (for example the *Year Book of Anesthesia* or *Survey of Anesthesia*) they leave one with the feeling that only a part of each story has been told. Each reviewer's comments are coherent and succinct, and occasionally a further reference is cited.

As the number and quality of anesthesia journals increases, it is increasingly difficult to remain "well-read." This compilation of papers is extracted from a body of literature little perused in the United States. Ignoring the larger body of international research inhibits one's own development and the advancement of the specialty as a whole. Application of the blinkers of a computerized literature search and reliance on a computer's literal minded interpretation of your needs is equally dangerous. Here we have a useful entry into an important but relatively inaccessible store of knowledge.

Trainees, established practitioners, and researchers need access to texts such as this so they can browse and gain a wider appreciation of current trends in research and the foundations of anesthetic techniques.

While not recommended as an addition to every anesthesiologist's bookshelf, any or all of this series would be an appropriate addition to departmental libraries for those whose curiosity goes beyond tomorrow's operating list.

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Manual of Anesthesia in Cancer Care

W. S. Howland, S. M. Rooney, and P. L. Goldiner, eds. New York: Churchill Livingstone, 1986, 321 pp, $27.00.

Most anesthesiologists practicing in the United States occasionally will be faced with the challenge of providing anesthesia for cancer patients during surgery. If these patients are treated early in the course of their disease before major physiologic abnormalities have occurred, few differences in management will be required; however, after various forms of therapy have been applied or the disease has progressed, anesthetic management may be significantly altered. The authors of this publication state in the preface, "a major purpose of this text is to orient the non-oncologic anesthesiologist not only to the possibilities of cure but to the myriad physiologic abnormalities that can occur in cancer patients." In this they succeed.

The first four chapters present a brief discussion of the various types of tumors, immune deficiencies, and complications of chemotherapy. This is the most interesting and unusual portion of the text in that it discusses those physiologic, metabolic, and electrolyte disturbances produced by cancer and its therapy that may affect the conduct of anesthesia. Some pertinent examples are 1) cardiac necrosis secondary to cyclophosphamide, busulphan, 5-fluorouracil, doxorubicin, daunorubicin, and mitomycin; and 2) the pulmonary toxicity of cyclophosphamide, chlorambucil, busulphan, melphalan, BCNU, CCNU, methotrexate, 6-mercaptopurine, azothioprine, cytosine arabinoside, bleomycin, mitomycin, and procarbazine.

Most of the authors' recommendations agree with my own. However, on page 147, the authors indicate that solution of the microaggregate problem requires routine use of a 40-micron filter. This is still a debatable problem. Another area of question is the management statement (p. 152) that they do not routinely administer platelet concentrates but offer no criteria for when they are appropriate.

The remainder of the text is a review of anesthetic considerations in the surgical treatment of any critical care patient, with extensive reference lists. Some of the techniques recommended may not be feasible for everyone, such as using the thromboelastograph to monitor coagulation. The closing chapter presents a discussion of several cases from the authors' institution, to illustrate their principles of management.

To the anesthesiologist who occasionally anesthetizes a patient for cancer surgery, this manual offers insight into some of the special problems that may be encountered.

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Consent to Treatment: A Practical Guide

F. A. Rozowsky. Boston: Little Brown and Company, 1984, 698 pp, $75.00 (including supplements 1985, 1986).

"Many people think of consent to treatment as a form. Consent is equated in their minds with a document through which patients agree to procedures their physician believes are advisable or necessary. Such a definition is incorrect and misleading, and in some instances can be dangerous . . . Consent is a process, not a form." In these opening lines, the author clearly delineates her concept of consent in medicine and in the ensuing 600 plus pages of this book proceeds to describe in detail the case law that defines the current concepts of informed consent. In the forward to this book, William J. Curran (Professor of Legal Medicine, Harvard University) notes that "the doctrine of informed consent has developed in the United States from a simple concept to an extremely complex body of law. It has become an area to be feared by every practicing physician and every medical research investigator." He further goes on to say that "in this book, the author presents a broadly comprehensive, deeply detailed, yet very practical guide to practitioners concerning the demands placed upon them by American law in this field. I am greatly impressed by the scope of this work . . . This is without doubt the most comprehensive coverage I have ever read in one volume concerning the doctrine of informed consent."

The author begins her book by discussing the legal concept of consent to treatment—the traditional approach, which is based on assault and battery, as well as the more modern approach, which is based on negligence theory. She then outlines the rules for valid consent, particularly the issues of coercion and undue influence and the problems related to legal capacity and mental capacity. She spends a great deal of time on issues concerning the answering of the patient's questions and of the various valid forms of consent. She attempts to define the patient's right for basic information as well as the information that need not be disclosed. She then defines the elements of negligent consent litigation and how one can defend against this type of lawsuit. In other chapters, she deals with consent related to women and reproductive matters, prisoners and detainees, minors, patients with mental illness, and mental retardation. She devotes an entire chapter to the right to refuse treatment, with an extensive comparison of the difference between curable but life threatening and terminal illness. She also discusses the law concerning living wills and patient directives, and, in particular, patients with religious objections to treatment. The final chapters of her book deal with human research and experimentation, organ donation and autopsy, and finally, the documentation of consent and practical rules for consent. Supplements to the initial 1984 edition were published in 1985 and 1986. Supplements are keyed, paragraph and page number to the original text. The publisher reports that the supplement for 1987 is in preparation and that the cost of the book includes the supplements published to date.

As noted above, the author's coverage of consent is comprehensive. Despite the fact that I am not a lawyer, I found the writing to be lucid and the arguments comprehensible. Each major chapter and section contains a summary of the important points, and the development of the material is logical. The weakest sections of the book were the sections on experimentation. I personally find the documentation provided by the National Institutes of Health to be more comprehensive and useful.

This is not a book for every practitioner of anesthesia. There was only one direct reference to anesthesia in the entire book. However, the concepts and concerns raised would be of interest to many anesthesiologists and to all those involved with anesthesia policy within the hospital, particularly the basis of consent for anesthesia. Thus clinical chiefs, department chairmen, and those involved with risk management would find this book to be of significant value with respect to those activities.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Altura BM, Halevy S, eds. Cardiovascular Actions of Anesthetics and Drugs Used in Anesthesia, Vol 2, Regional Blood Flow and Clinical Considerations. Basel: S Karger AG, 1986, 296 pp, $119.50.

Azar I, ed. Muscle Relaxants, Side Effects and a Rational Approach to Selection, Volume 7 in Clinical Pharmacology Series. New York: Marcel Dekker, 1987, 238 pp, $83.50.

Blacher RS, ed. The Psychological Experience of Surgery. New York: John Wiley & Sons. 1987, 236 pp, $31.50.

Cottrell JE, Turndorf H, eds. Anesthesia and Neurosurgery, 2nd edition. St. Louis: CV Mosby, 1986, 530 pp. $75.00.

Droh R, Spintge R. Closed-Circuit System and Other Innovations in Anaesthesia. New York: Springer-Verlag, 1986, 253 pp, $54.29.

Feldman SA, Scurr CF, Paton W, eds. Drugs in Anaesthetic Practice: Mechanisms of Action. Baltimore: Arnold, 1987, 456 pp, $79.50.

Gallagher TJ, ed. Advances in Anesthesia, Volume 1. Chicago: Yearbook Medical Publishers, 1984, 445 pp, $55.95.

Gelman S, ed. Anesthesia and Organ Transplantation. Philadelphia: WB Saunders, 1987, 254 pp, $49.95.

Jardin F, Dubourg O. L'Exploration Echocardiographique en Medecine D'Urgence. New York: Masson, 1986, 156 pp.

Menitove JE, Kolins J, eds. AIDS. Arlington, VA: Amer Assoc Blood Banks, 1986, 106 pp, $17.00.

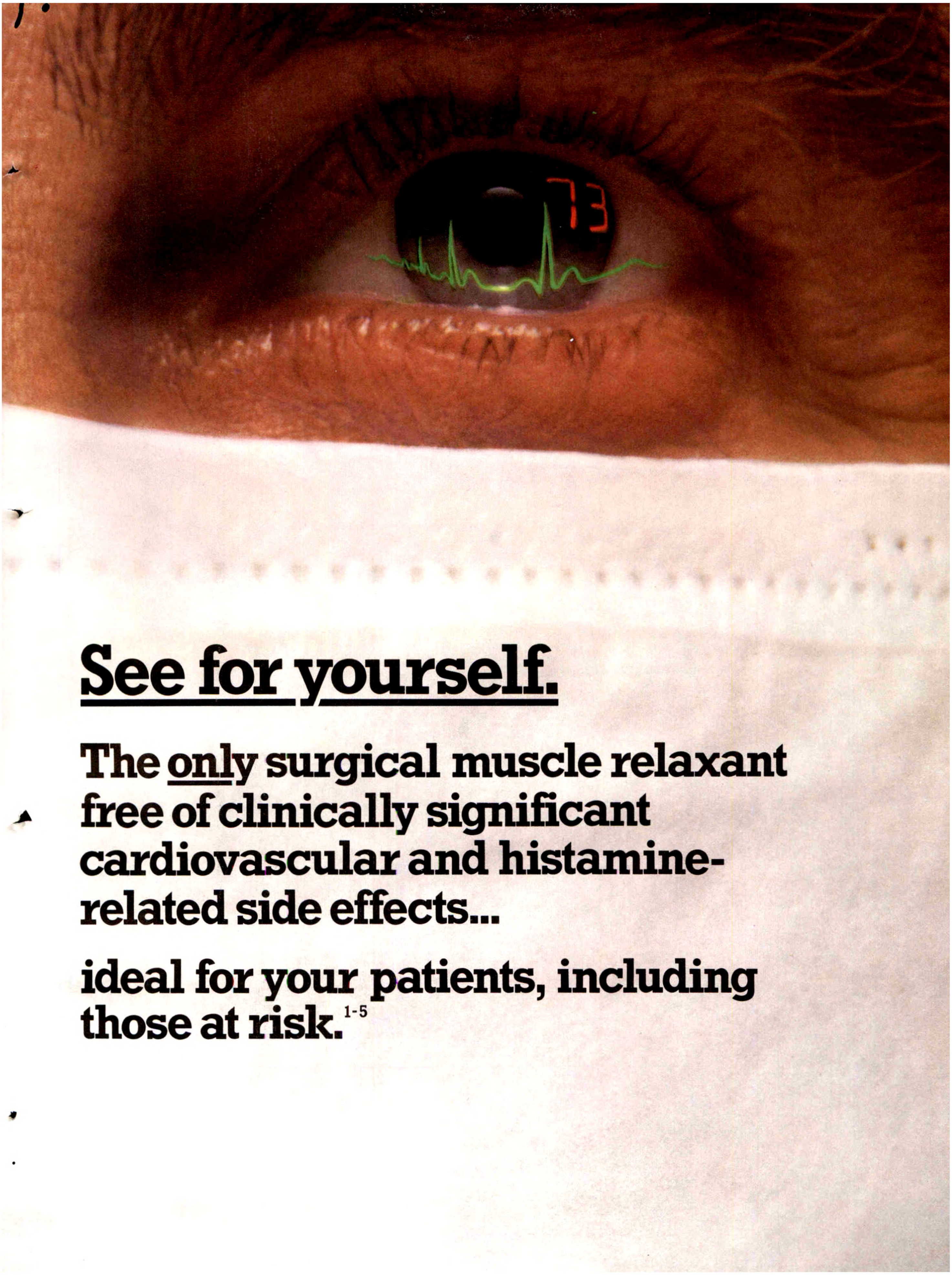
Petty C. The Anesthesia Machine. New York: Churchill Livingstone, 1987, 234 pp,. $29.50.

Reynolds AW, Steckler D, eds. Practical Aspects of Blood Administration. Arlington, VA: Amer Assoc of Blood Banks, 1986, 105 pp, $19.00.

Shoemaker WC, Abraham E, eds. Diagnostic Methods in Critical Care. Automatic Data Collection and Interpretation. Vol 9 in the Basic and Clinical Cardiology Series. New York: Marcel Dekker, 1987, 528 pp, $69.75.

Snyder JV, Pinsky MR, eds. Oxygen Transport in the Critically Ill. Chicago: Yearbook Medical Publishers, 1987, 554 pp, $74.95.

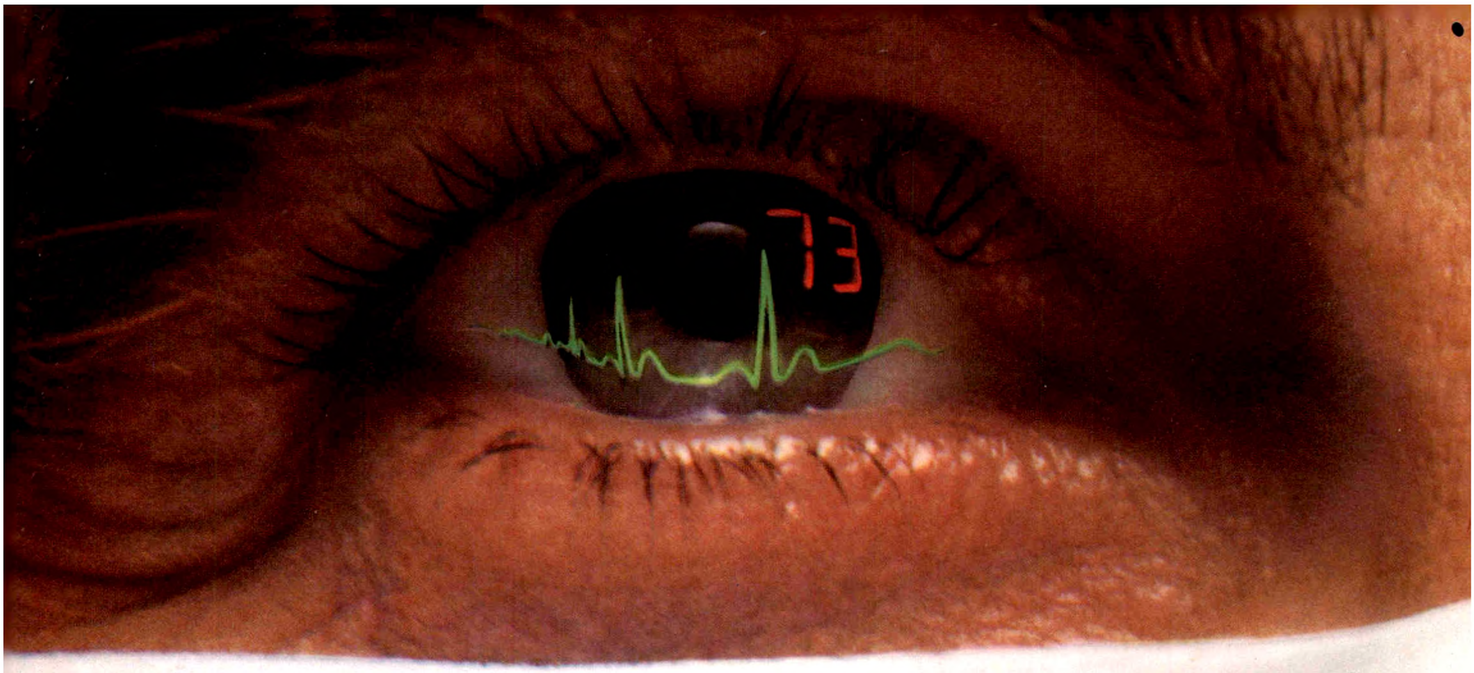
Taylor AE, Matalon S, Ward PA, eds. Physiology of Oxygen Radicals. Bethesda, MD: Amer Physiological Society, 1986, 301 pp, $49.50.



See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

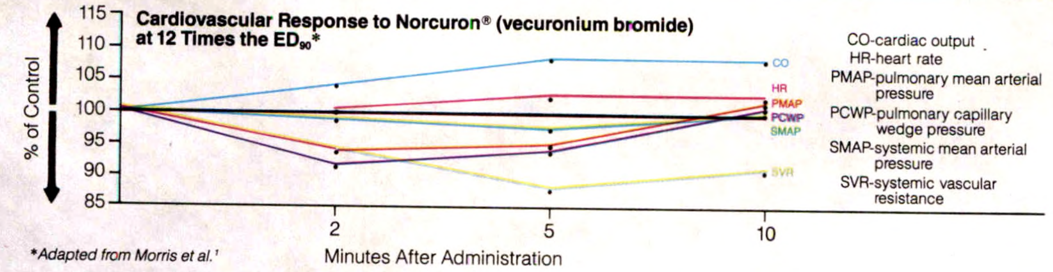
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



Cardiovascular Response to Norcuron® (vecuronium bromide) at 12 Times the ED_{90}*

*Adapted from Morris et al.[1]

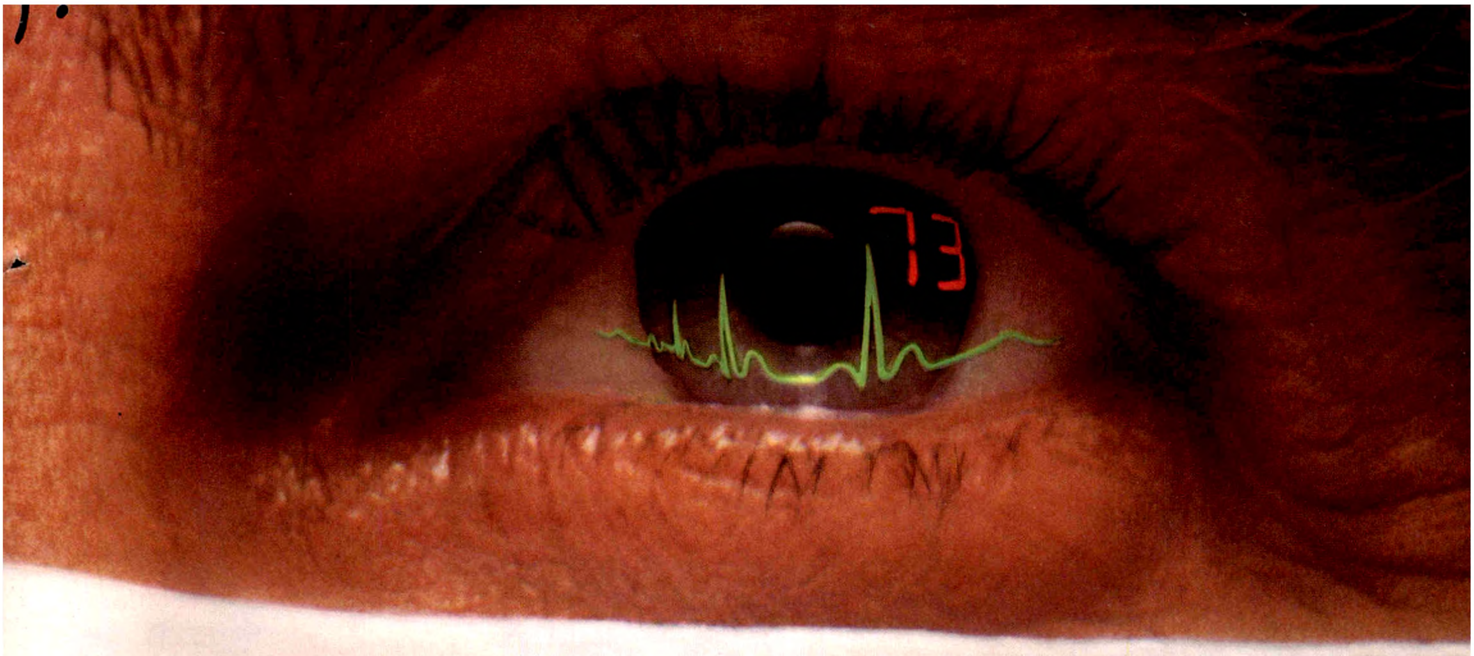
Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

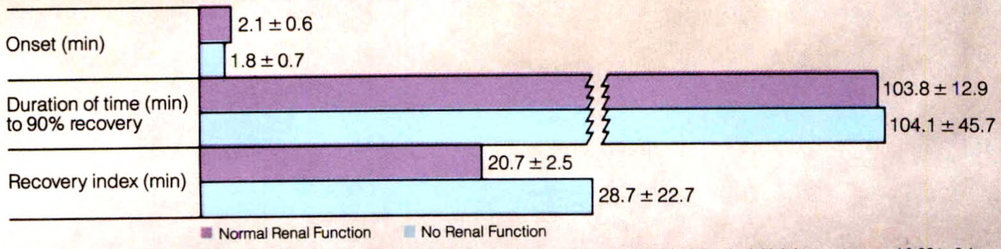
*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



** Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.*
† Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®
(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

NO
REFRIGERATION
REQUIRED

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringer's

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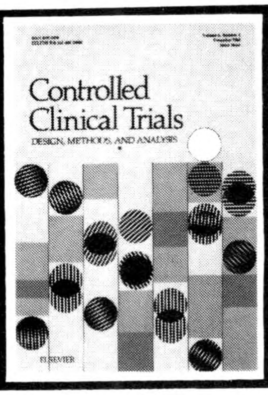

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Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

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6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC **0094-0037-05-Hespan*** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION

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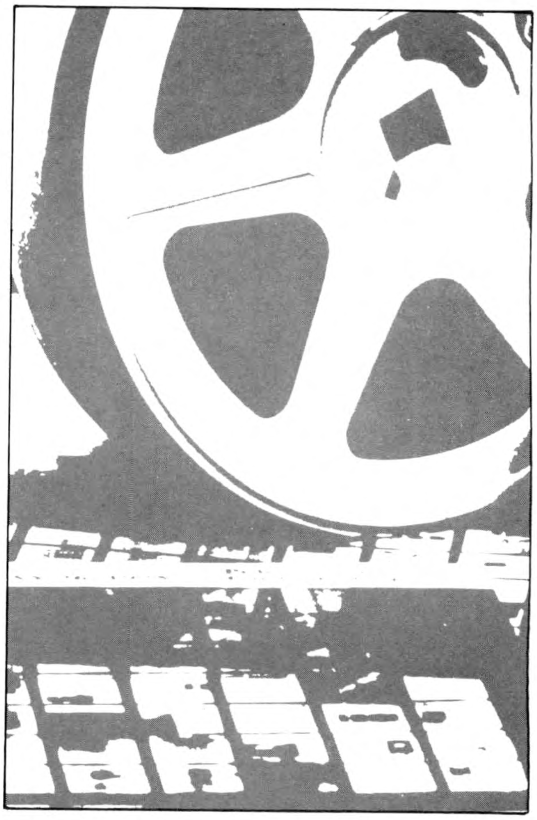

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- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
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***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiolo 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophoniu Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

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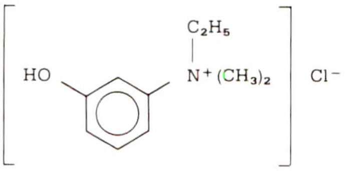
Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

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Send name, address, and phone to Box ANA 5-84-E, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510. Or phone 718-727-9690.

SOUTHWESTERN PA ANESTHESIOLOGIST
BE/BC to join group. All except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ORAL BOARD REVIEW
Practice exams with critique. Intensive weekend course in Tampa, FL. Next class Sep. 11–13. Two instructors. Limited class size. Reply: 2656 Gunckel Bl., Toledo, OH 43606, or (419) 475-9641.

NORTH CAROLINA
Anesthesiologist needed to join fee-for-service group. Full partnership after year on salary. Send CV to Box BB10, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

MIDWEST PAIN MANAGEMENT
Expanding Midwest anesthesia practice seeks anesthesiologist trained in all aspects of pain management to join group as associate. Opportunity to establish a new service with support structure of established group. Send CV to Box CC13, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

MIDWEST CRITICAL CARE
Expanding Midwest anesthesia practice seeks anesthesiologist trained in critical care medicine to join corporation as mainstream associate. Duties to include physician-in-charge of an ICU unit, teaching and the clinical practice of anesthesiology in a tertiary medical center. Send CV to Box CC14, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

TEXAS
Two board eligible/certified anesthesiologists to join PA group of six boarded MDs to form all-MD anesthesia service in 300-bed Catholic hospital in community of 160,000. No OB; mainly cardiovascular, neuro, ortho and general surgery. Generous financial arrangements; partnership available when boarded. Recreational activities and cultural arts plentiful. Five-hour drive to mountains/skiing. Position available 7/1/87. Send CV to Box CC12, ℅ *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

UNIVERSITY OF CALIFORNIA, IRVINE
is seeking a senior faculty person to serve as Chief of Anesthesia Services for the Veterans Administration Medical Center in Long Beach. This service is part of the integrated Anesthesia Residency training program at the University of California, Irvine. Interested applicants should have experience in basic and clinical research, administration and resident training. Research space and funding are available. Salary is commensurate with the position. Candidates must be Board certified and be eligible for a California State license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Kevin K. Tremper, PhD, MD, Chairman, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Rt. 81A, Orange, CA 92668.

RESEARCH FELLOWSHIP
The W.E. Spoerel Fellowship has been established by the Department of Anaesthesia to encourage training of clinical investigators. A research training program, organized jointly by the Departments of Anaesthesia and Pharmacology and Toxicology, will lead to either an MSc or PhD degree. Renumeration will be based on the pay scale of MRC Fellows for the appropriate level of experience and $5000 per annum will be available for research expenses. The Fellowship will be granted for 1 year and renewable for up to 3 years with annual evaluation of progress. Applications for July 1, 1987, and July 1, 1988, are invited from anesthetists in training or those who have completed their training within the past 3 years. Scientists at the postdoctoral level may also apply. Please reply in writing, including a current curriculum vitae to W.A. Tweed, MD, FRCP(C), Professor and Chairman, Department of Anaesthesia, University Hospital, 339 Windermere Road, London, Ontario, Canada N6A 5A5.

OB ANESTHESIOLOGIST
A 400-bed Texas hospital is recruiting an OB Anesthesiologist to complement current OB Anesthesia Services. The Hospital currently has 3000 births per year and offers high-risk delivery and neonatal intensive care services. The candidate shall have experienc in general and regional anesthesia with emphasis on obstetrical epidural anesthesia Please submit curriculum vitae to Box D23 ℅ *Anesthesia and Analgesia*, 333 Cedar Street New Haven, CT 06510.

ANESTHESIOLOGIST
233-Bed teaching hospital with residents i Surgery, OB/GYN, Internal Medicine, an Family Practice seeking two Staff Anesthesiologists—one to be appointed as Chief Department of Anesthesiology. Candidate should be Board Eligible or Certified i Anesthesia and have experience in critica care anesthesia, epidural and pediatri anesthesia. Salary negotiable depending o experience. Hospital located in beautiful Sa Joaquin County, close to major cities an skiing. Submit CV and references or contac Nathaniel M. Matolo, MD, Director of Surgery, San Joaquin General Hospital, PO Bo 1020, Stockton, CA 95201. Phone: (209) 460 6600. AA/EOE.

DELAWARE
Immediate opening for BC/BE anesthesiologist in group at an 1100-bed university affiliated tertiary care medical center. Al major surgical specialties. Recent fellowship training preferred. Unusual opportunity with excellent benefits and early partnership. Send CV with references t Anesthesia Services, P.A., 3513 Concor Pike, Wilmington, Delaware 19803.

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum ¼ page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: **$1.00 per word, minimum twenty words. Additional fee of $12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed **in duplicate** to:

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Make checks payable to Elsevier Science Publishing Co, Inc.

KENTUCKY
The Department of Anesthesiology, University of Kentucky in Lexington is seeking additional faculty. We are recruiting two qualified physicians to direct the outpatient and pediatric anesthesia programs and a second faculty member for our pain management program. Applicants must be board eligible/certified, interested in medical student and resident teaching as well as clinical research. Excellent salary and fringe benefit program. Please reply with curriculum vitae to William O. Witt, MD, Chairman, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, KY 40536-0084.

TENNESSEE; ANESTHESIOLOGIST
Private hospital group practice seeks BC/BE Anesthesiologist. All types of high-risk surgical procedures except OB and OH. Additional training in cardiovascular or neuroanesthesia is advantageous. Send CV to Anesthesiologists Group, P.C., PO BOX 50578, Nashville, TN 37205.

CHIEF OF ANESTHESIOLOGY/STAFF ANESTHESIOLOGISTS
BC/BE immediate opening at San Francisco Bay Area Trauma Center/County Teaching Hospital. Staff includes seven MDs, six CRNAS. CV to John Lennox, DO, Highland General Hospital, 1411 E. 31st Street, Oakland CA 94602—an Equal Opportunity/Affirmative Action Employer.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:
Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117.

ANESTHESIOLOGIST
JCAH-approved hospital. No OB or OH. Join 5 anesthesiologists. Professional Corporation. Excellent department and environment. Contact Holyoke Anesthesia Associates, 575 Beech St., Holyoke, MA 01040. (413) 532-9129.

ANESTHESIOLOGIST
Full-time position at Instructor or Assistant Professor level with the University of Louisville. Must be board eligible and meet Kentucky licensure requirements. Competitive salary and fringe benefits. Applicants please send curriculum vitae to B. M. Rigor, MD, Chairman, Department of Anesthesiology, School of Medicine, University of Louisville, Louisville, Kentucky 40292. The University of Louisville is an Affirmative Action, Equal Opportunity Employer.

TENNESSEE
Anesthesiologist: Fulltime positions at level of Instructor/Associate Professor level with emphasis on teaching, patient care and clinical research. Prerequisite: meet Tennessee license requirements and ABA diplomat or eligible for ABA examination. Prefer interest and experience in teaching and patient care. Excellent opportunity for an anesthesiologist who wants an ideal mix of private practice with teaching and clinical research. Send curriculm vitae, bibliography and the name of at least three references to John J. Angel, MD, Acting Chairman, Department of Anesthesiology, The University of Tennessee, Memphis, 877 Jefferson Avenue, Chandler Bldg. Room FG25, Memphis, TN 38138. AA/EEO Employer.

ANESTHESIOLOGISTS & CRNAs
Are you ready for "New Beginnings"? John Paju, CRNA, has been successfully placing his colleagues (both MD and CRNA) into hundreds of temporary and permanent positions throughout the US since 1969. For that personal and helpful touch call John or one of our Placement Coordinators at 1-800-FAST-GAS to discuss exciting job potentials. Send your resume to 619 South State Street, Ukiah, CA 95482. Placements are paid by the employer!

PENNSYLVANIA
Chief of Anesthesia to head department serving 200-bed community hospital in south central Pennsylvania. Board certification and administrative experience. Fee-for-service practice. Well-equipped department. All types of surgeries except heart. Position includes active practice of anesthesiology and responsibility for quality assurance standards and smooth operation of anesthesia services. Easy access to major cities. Good schools, recreational and cultural facilities. Send CV to Lawrence Scanlan JR, President, Community General Hospital, Reading, PA 19601.

ANESTHESIOLOGISTS
Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

PAIN MANAGEMENT
Unique opportunity for BC/BE Anesthesiologist with clinical ability to join progressive group of anesthesiologists. Practice limited to Pain Management. No OR or OB anesthesia. All procedures for treatment of pain including transphenoidal pituitary adenolysis and implantable reservoirs. Strong ancillary support services including full-time psychologist. Applicant should possess a strong interest in regional anesthesia and desire one-on-one patient contact. Willing to train right individual. Excellent salary and benefits. Send CV to Pain Consortium of Greater KC., 8301 State Line, Kansas City, MO 64114.

IMMEDIATE OPENING
For BC/BE anesthesiologist to join group in semirural college community located in northwest Pennsylvania. No OH, no neuro. Interest in pain desirable. Send CV and three references to PO Box 1434, Meadville, PA 16335.

MASSACHUSETTS
Due to expansion and retirement, the Anesthesia Service at Salem Hospital is seeking a BE/BC anesthesiologist to join our group to provide services at a progressive community hospital just north of Boston. All surgical specialties except OH. We offer a competitive salary and excellent fringe package, as well as the opportunity of working with a group of university-trained, board certified physicians. For further information, contact Dr. Jeffry Brand, Chief, Anesthesia Service, Salem Hospital, 81 Highland Avenue, Salem, MA 01970.

CHIEF OF ANESTHESIA
To head department serving 216-bed community hospital in Baltimore. Board certification required with administrative experience preferred. Position includes active practice of anesthesiology and responsibility for quality assurance standards and smooth operation of anesthesia services in a busy OR. Reply to Box DD22, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

PERMANENT POSITION WANTED
CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST
Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

NEAR COLUMBUS, OHIO
Anesthesiologist for FFS private practice in a modern, well-equipped, 225-bed community hospital. Busy surgery schedule. Coverage from two other anesthesiologists. First year minimum guarantee of $120,000. Lovely area, major university nearby. Relocation and interview expenses paid. Reply to Box EE24, % *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

ANESTHESIOLOGIST
Board certified or eligible to join a group of five Anesthesiologists and six Nurse Anesthetists. 350-bed modern hospital in Fredericksburg, Virginia. One hour from Washington, D.C. Reply to Dr. Robert A. Kravetz, 2101 Fall Hill Avenue, Fredericksburg, VA 22401. Or phone (703) 371-2786.

ROCKY MTS./SOUTHWEST
We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

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